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Ontario

ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

Hearing held
21st floor
180 Dundas Street West
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange	Commissioner
P.S.A. Lamek, Q.C.	Counsel
E.A. Cronk	Associate Counsel
Thomas Millar	Administrator

Transcript of evidence
for

June 5, 1984.

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Hearing held on the 21st Floor, 180 Dundas Street West, Toronto, Ontario, on Tuesday, the 5th day of June, 1984.

- - - -

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOT - Registrar

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E R R A T A

June 4, 1984.

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Page 68, line 22 - Mr. Young should read Mr. Hunt

Page 107, line 20 - Mr. Young should read Mr. Hunt

M/ko

--- Upon commencing at 10:00 a.m.

THE COMMISSIONER: Yes Mr. Lamek.

ARGUMENT BY MR. LAMEK: (Continued)

When I finish this part of the argument I expect in the early part of this morning, sir, and Miss Cronk takes over the torch from me I am going to ask to be excused so I can wheeze and sneeze somewhere else.

First, with respect to yesterday Mr. Commissioner, you were entirely right, there is only one child where no member of the Trayner team was present for onset of critical symptoms or death. I think you identified the child as Leith and that I understand to be right.

Second, with respect to the question of what Dr. Freedom said to Mr. McGee about the ordering of a post mortem dig. level on the Baby Estrella, the reference that I had in mind but had mis-transcribed is in Volume 30 beginning at page 5647 at line 14, where in cross-examination by Mr. Percival the following exchange took place. There had been a reference to Dr. Taylor's evidence about the conversation at nighttime with Dr. Freedom:

"Q. And you gave evidence at - very briefly that you had absolutely no

"recollection of this conversation
with Dr. Taylor?
A. That's true.
Q. And that is as far as it went?
A. Right.
Q. That was on February 19th, 1982.
Do you recall prior to that though,
in a meeting with the Crown
Attorneys Mr. McGee and Mr. Wiley,
on December 1st of 1981, at which
conference Mr. Ortved, your Counsel,
was present to go over your evidence?
A. Right.
Q. And do you recall on that occasion
on December 1st of 1981 saying this to
Mr. McGee and Mr. Wiley: 'The dig.
level ...'."

And there is then an exchange as to what it is Mr. Percival was reading from and it turns out to be the notes made by Mr. Wiley of which a copy had been provided. Continuing at line 17:

"'The dig. level was taken on
Estrella. The resident, a Dr. Taylor,
called and told me about the death of
Estrella. I asked if Estrella was

"on dig. I asked him to get another level, there had been a high level ante mortem.'

Is that your recollection of what your told Mr. Wiley?

A. No.

Q. And Mr. McGee on December 1st of 1981?

A. My recollection was that I had been informed that Dr. Taylor had said that I had requested him to do all this, and I was echoing back, I don't remember this, I don't remember that Dr. Taylor had asked me to do any of this.

Q. So do I take it that the notes, if they are notes of Mr. Wiley, are inaccurate in relation to what you recall on December 1st of 1981?

A. Yes. I specifically recall being somewhat surprised by this and again echoing back, I have no recollection of that phone call."

It seems, therefore, that Dr. Freedom denied having said what was recorded in the Crown

Attorney's notes in the meeting of December 1981. The notes, however, did attribute the statement to him. I suppose one has to wonder how that came about especially in the light of the character that Dr. Freedom attempted to put on his statement to the CBC radio interviewer. As I said yesterday, Mr. Commissioner, I don't think a great deal turns upon that, clearly one way or another, and I suggested Dr. Taylor's evidence is to be preferred, a sample was drawn from Estrella in circumstances of which we are aware and yielded a level of which are aware.

I completed at the end of the day yesterday, sir, the very broad outline chronology of the events with which we have been concerned. I propose to turn quite briefly now to a general review of certain theories that have been advanced from time to time in attempts to explain what happened on the cardiology wards in the period under review. I hope that in addressing those theories, sir, I am not going to be accused of putting words into anyone's mouth, or of attributing to anyone a theory that he or she did not in fact advance. I don't know which if any of these theories will be seriously advanced in the course of argument, but in light of what has gone before to this point whether the theories are put forward or not

at this stage as possible explanation for the events in the epidemic period it seems to me they will have to be dealt with whether briefly or extensively in your report and I, therefore, address them briefly now.

The first is the theory, if I can put it this way, that nothing really happened at all on Wards 4A/B in the nine month period. Notwithstanding Dr. Rowe's acknowledgement that deaths on the ward as opposed to deaths in the ICU or in the OR were generally speaking the exception, and notwithstanding that nurses were clearly concerned at the high number of deaths, and that was a concern which the cardiologists themselves took active steps to allay. Notwithstanding all of that, it seemed at an early stage of our proceedings that the Hospital was taking the position that nothing had really happened at all. That is to say that although starting in the summer of 1980 there was an apparent increase in the number of cardiology ward deaths there was no significant actual increase in mortality to be concerned about.

You will recall that during his cross-examination, or the examination of Dr. Rowe, my learned friend Mr. Scott referred to and marked as an exhibit, it was No. 125, a chart or a graph which was said to

show deaths in a number of different areas in the hospital and in the hospital as a whole. It was a glorious multicoloured thing and colour coded. As I understood it, the intention of that chart was to show that the apparent increase in the wards 4 A/B deaths was merely a blip on the graph, just like any other blip on any other one of the other lines on that chart.

Now after Dr. Rowe left the witness box we never heard another word about the chart. In my submission it is simply not a tenable position to assert that whatever was happening on the cardiology wards was no more than a fluctuation in the mortality rate of a kind that inevitably occurs in any area of the hospital from time to time. There are three bases for the submission that is simply an untenable position.

First, the epidemiologists from Atlanta and from the Ministry of Health had no question but that there was during the epidemic period a mortality rate that was utterly unprecedented on the cardiology survice, and which showed a statistically significant variation from the norm for those wards, and that was a view with which the Hospital's epidemiologist consultants did not disagree as I understood their report.

Second, it is not merely the leap

in the rate of ward deaths that suggests that something unusual was indeed happening. The other features of the epidemic period deaths also call for an explanation of some kind. The deaths in the middle of the night; the sudden and irreversible decline seen in so many of the children; a decline that could not be reversed by even the most heroic of resuscitation efforts; the association of the deaths with one or more members of a single nursing team. Those in my submission are elements which cannot be ignored in deciding at the outset whether there was something occurring that called for investigation.

In my submission it is extremely difficult to accept that there was a greatly increased death rate with all of these other coincidences and patterns and that it all occurred quite naturally and that nothing unusual was really happening.

The third basis for my submission that the view is an untenable one, is that the clear evidence in a small number of cases, even in only one case, that unauthorized doses and/or amounts of a dangerous drug had been given to children makes it impossible to accept without the closest scrutiny the proposition that nothing was happening.

If I could just refer to one of the

elements in the total picture which has to be explained as this business of the nighttime deaths, sir. I referred on other occasions yesterday to the strikingly large percentage of deaths which occurred between the hours of 1 o'clock and 5 o'clock, or when the onset of terminal events occurred in that period.

Now the available statistics, and I am referring for example to Exhibits 35, 36 and 37 which are charts prepared by Dr. Gilmour Bryson, show very few deaths indeed in that middle of the night period in any of the other nine month periods examined outside the epidemic period. Whether that middle of the nighttime period was defined in terms of 1 o'clock to 5:00, midnight to 4:00, or midnight to 6 o'clock, the result is essentially the same, in no other nine month period was there ever more than three deaths occurred in that time span, and a very striking feature of the epidemic period of course is the very large number of deaths that did occur in that time span.

In my submission that kind of departure from the historical norm makes it difficult to accept that nothing at all was happening on the ward. I said it earlier, Mr. Commissioner, but it may be instructive to enquire about the other side of that coin. Having observed that so many deaths occurred in the middle of

the night it may be useful to wonder why so few deaths in the epidemic period occurred during the day or the early evening, and a clue to that may be in the impression that Dr. Rowe related as having been an impression of the cardiologists in the fall of 1980 that the wards were understaffed at night.

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When he was pressed - I don't have the reference now but I can provide it to you, sir - he said his impression was that there were more people around during the day than there were at night. And indeed there were.

The evidence you have heard makes it clear that during the daytime there are in addition to the normal nursing complement that we find at night, student nurses, head nurses, nursing specialists, staff physicians, parents. The evidence is that a ward during the day is a very busy place indeed. Lots of people around.

Of course if a child is going to perfectly naturally and as a result of his clinical condition, if a child is going to go into a sudden and irreversible decline and die, it really doesn't matter how busy the ward is. If the child's condition has reached the point where that is going to occur as a matter of natural course, then it is going to happen. And if the deaths were natural it is puzzling to know why the sudden declines didn't occur during the daytime as well.

The ward at night as you have heard is a rather different scene; it is very much

quieter in terms of traffic as well as literally quieter. Relatively few people around. One has to say that if one were engaged in nefarious conduct the risk of detection had to be very much smaller at night than during the day.

The lack of daytime deaths does not in my submission support an innocent or natural characterization of the deaths that occurred. One would expect random occurrences around the clock if these were natural deaths. The absence of daytime deaths in the circumstances of the daytime traffic on the ward and the very high incidence of nighttime deaths at times of relatively low traffic on the ward, from both sides of the coin are suggestive of a non-natural cause of death.

Mr. Commissioner, another suggestion that from time to time has been raised is that in cases where we have more or less clear pharmacological and toxicological evidence here we may well be dealing with a whole series of unfortunate, indeed tragic medication errors, which may have been responsible for the deaths or at least for the recorded digoxin levels.

In my submission it is very difficult - indeed it is impossible to deny that

medication error may indeed have been responsible for one or more of the deaths that are under review. I will deal at a later stage with the individual cases where drug error has been expressly suggested. One cannot rationally exclude the possibility that drug error may indeed have been involved in one or more of these cases.

Although I will deal with the case of Justin Cook later I say now it is difficult at first blush to see how a drug error could have occurred with respect to that child in the circumstances of the care he was receiving and in light of the pharmacological evidence which we have had. But I have to concede that almost any one of those babies could have died as a result of medication error.

To make that concession, however, in my submission is a very far cry from conceding the possibility that all suspicious deaths or even all elevated digoxin levels or all levels of digoxin where none should have existed may reasonably be thought to have been attributable to medication error. In my respectful submission that conclusion again is simply not tenable.

In the first place it could not be

regarded as a plausible explanation unless a number of other phenomena could also be explained. For example, why if they were errors were such errors occurring primarily at night when as we have heard there is far less hustle and bustle on the ward than during the day? On Dr. McGee's evidence one would have thought daytime errors were far more likely than nighttime errors.

Second, why if these were errors, why were such errors presumably in many cases producing death which only occurred when one or more members of a particular nursing team were on duty? And again if members of that team had a propensity either to make or to encourage others to make medication errors, why did that propensity only flower at night?

Third, there would have to be some reasonable explanation as to how one may reconcile the repeated medication error theory with a clear view of the experts that medication errors rarely cause death. I refer in that regard to the evidence of Dr. Mirkin, in volume 88, page 9075, Dr. Bain, in volume 63, page 4096, and Dr. Kauffman, in volume 71, page 5663 and in volume 83, page 8101.

One would also need to explain how it could repeatedly happen that errors of a kind which even proponents of the error theory would concede to be unlikely should occur. For example, errors including the substitution of multiple vials of medication A for a single vial of medication B. Dr. Spielberg conceded that once you get into multiple vial errors the possibility of error becomes very much smaller.

Errors made by more than one person combined to produce a tragic result, the drugs which had to be double checked, and so on. The scenarios, the sequence of and the number of errors that had to combine to produce a particular result have been put to several witnesses, and I am sure you recall them, Mr. Commissioner. That, too, would have to be explained satisfactorily before the medication error theory for these deaths could begin to be acceptable.

At the end of the day, how? It would need to be explained how if there is compelling evidence of deliberate overdose in respect of even one child, how a speculative theory of medication error can be regarded as a satisfactory explanation of other deaths. And if there be such

evidence with respect to one child - and I will be dealing with that at a later stage - that in itself in my submission writes an end to the medication error theory as an explanation for the multiple deaths.

In short, Mr. Commissioner, in my submission this medication error explanation for all or even for a substantial number of deaths is simply too fragile to overcome all of the obstacles to its acceptance.

Third, we have heard about the possibility of the mysterious and unseen visitor to the wards in the middle of the night. When I say "unseen" that may mean literally unseen or unnoticed in the sense that a person's presence was not thought to be remarkable.

Again dealing very briefly with that in my submission it is not a theory which is plausible. It is extremely difficult to believe in the first place and generally how such a mysterious visitor would have the extraordinary good fortune to visit a ward, visit a ward and find a child unattended and unattended for sufficient time to do whatever needed to be done, or to remain unseen or unnoticed until a child was

unattended. Again one would have to ask why such a visitor would appear only when Mrs. Trayner's team was on duty. And third, how did that visitor work his evil magic with children who were on constant nursing care?

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RD/hr

Mr. Commissioner, we will move to another proposition. It may well be advanced but there has been some discussion of it in the course of the evidence. A proposition may be advanced but unless there is clear and compelling evidence to the contrary any death not in the opinion of the medical experts was consistent with the child's clinical condition, must be assumed to have occurred naturally. Really the question is where the onus lies in approaching a particular death, whether one assumes natural death in the absence of compelling evidence to the contrary, or whether one starts from a different vantage point.

It is my submission that that is not an assumption that you should automatically feel obliged to make merely because there maybe unclear pharmacological or toxicological evidence about a child, or indeed, no such evidence at all.

I suggest, Mr. Commissioner you are obliged to consider all relevant evidence and that may fall under either or both of two headings: first, and obviously evidence as to the particular child, particular clinical condition of the child and its severity and prognosis; the child's course in the days and hours preceding the onset of critical

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terminal symptoms; the nature of the child's terminal episode, symptoms, behaviour and so on; the responses of physicians and nurses to the child's death. Were they surprises, puzzled, distressed? All of the individual features of the child's case, but in addition the second kind of evidence, the evidence as to patterns and common threads running through the deaths. At the time of the onset of critical symptoms of so many of these children, the depressing failure rate of resuscitation efforts during the epidemic period, the observable associations between Hospital personnel and deaths, the remarkable frequency of sudden precipitated and irreversible decline to cardiac arrest and death.

With respect to those matters, Mr. Commissioner, I don't suggest the presence of any one of them in a particular cases is sufficient without more to justify a conclusion or even a suspicion but a death may have to be something other than natural, but if a child's death occurred suddenly, unexpectedly, surprisingly or without any satisfactory clinical explanation, and if there is no or only inconclusive toxicological and pharmacological evidence you may conclude, and in my respectful submission, you could properly conclude, that if that child suffered a

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sudden and irreversible onset of symptoms that are indicative of digoxin intoxication in the middle of the night, in the presence of one or more members of a particular nursing team, you may properly conclude, in my submission, that that death could be viewed as suspicious. At bottom, my submission to you will be this, that once you have concluded that any one of these children died of digoxin intoxication which, in all the circumstances was likely not the result of accident or mistake, once you make that conclusion with respect to any child, the balance, in effect, had tipped and you must then consider whether others, and perhaps many many others of the large number of children who died, may have suffered the same fate.

In giving that consideration to all of the deaths you are obliged, in my submission, to consider whether each death fits into a pattern made up of elements which are, themselves, not plausibly explained, except by an ugly and sinister rationale.

I suppose what I am really saying, Mr. Commissioner, is this: if you conclude that one death was the result of foul play one has to be suspicious that other of this very large number of deaths in this nine month period was similarly the

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result of foul play. One can no longer bring the same, for give the use of the expression, "innocence"to the other deaths in light of that conclusion that perhaps could have been brought to it without that conclusion.

I am suggesting that coincidence and bad luck are not plausible bases upon which to explain so many sudden deaths in the middle of the night and in the presence of one or more members of a single nursing team. I have to concede the possibility that all of those things befell the babies on that particular nursing team, by coincidence, by terrible luck, by bizarre and repetitive quirks of fate, and that all of those horrible and undirected forces came to a sudden and simultaneous end on March 22nd, 1981, I have to concede that is possible, but to state the possibility is, in my submission, to acknowledge its extreme remoteness.

Rational human beings direct their lives and form conclusions and judgements based upon what their good sense and experience tell them is probable and plausible, not on possibilities so remote as to be virtually negligible.

In my submission and in light of all the evidence that you have heard, the conclusion is

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inescapable. I shall detail this later. The conclusion is inescapable that babies were deliberately killed by overdoses of digoxin on the cardiology wards in the Hospital for Sick Children in the period from July 1980 until late March 1981. The question to which I fear we will never have a complete and certain answer is how many babies suffered that fate.

Sir, I hope that I may be able to be of assistance to you when I come to review the individual deaths, but I ask those at this point to hear Miss Cronk on matters relating to digoxin and pharmacological and toxicological evidence to refer.

THE COMMISSIONER: Yes. Will you take your cold away?

MR. LAMEK: If I may be excused I will do that, Mr. Commissioner.

THE COMMISSIONER: I wouldn't want you to affect everyone else with it.

Yes, Miss Cronk.

MS. CRONK: Thank you, sir. Mr. Commissioner, as Mr. Lamek briefly outlined, it will be my intent to review certain of the evidence given by the pharmacologists, the biochemists, Mr. Cimbura, the toxicologist from the Centre of Forensic Sciences

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and certain of the pathologists who have testified for the Hospital for Sick Children. I will do so, sir, for two purposes, in the hope that it will be of an assistance to you.

First, as a basis for submissions, which will later be made by Mr. Lamek concerning the significance, if any, to be attached to the actual digoxin levels and concentrations that were measured in tissue and blood specimens from certain of these children, and, secondly, as a basis for submissions which I will be making concerning the suggestion that there are problems or difficulties with either of the integrity of certain of the samples, themselves, the sampling techniques that were used, the analytical techniques that were used to measure the digoxin concentrations, all of which it might be said, have rendered certain of the results unreliable or unintelligible. Some of the matters which will be reviewed today, sir, with your indulgence, there is, in fact, no disagreement amongst the many experts that you have heard. On some issues there is a great variation in opinions held and, as well, in the level of confidence attached by the experts to the opinions which they have expressed. At times, sir, therefore, it may appear to be a summary or a review

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of much of the evidence on these basic pharmacological issues, rather than submissions designed to advance one position or another and where this is the case, sir, it is done for two purposes, first, to identify the areas of agreement amongst the experts, who testified before you, and secondly, the converse, to identify for you the areas of dispute, the areas where divergent opinions have been expressed.

In the hope that it might be of assistance to counsel and to you, sir, I have prepared an index to the subject areas of submissions that I will be making today. It has been made available to counsel. I provide one to you, sir, so there is at least some indication of where I intend to go and at what particular stage we are at during the course of the day. I believe it has already been provided to you, sir.

I propose, as you will see from the index, to deal first with the basic evidence that you have heard, concerning the drug, digoxin, itself, its function and effect. Some of the submissions you have heard from various pharmacologists as to the pharmacokinetics of the drug, and by that, sir, I mean the chemical and pharmacological evidence concerning the movement and pattern of behaviour of

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the drug in the body once administered, be it administered by intravenous or oral routes of administration and, as well, with certain of the evidence dealing with the therapeutic use of digoxin and, in particular, as it was used during the inquiry period in the Hospital for Sick Children.

M/ko

You will see as well, sir, that it is my intention to deal with the techniques, or the detection and measurement of digoxin concentrations and samples of all kinds, tissue and blood specimens. I propose to deal with the evidence that you have heard concerning the reliability of the various analytical techniques that are available given the current state of the art, and in particular to review, sir, and to make submissions to you concerning the proposition that what has been called before you substance X, and that is a dogoxin-like substance, may account for some of the levels that were realized in these children. Then to deal, sir, with the problems which are attendant on interpretation of the digoxin concentrations that are measured in various specimen types. Then to deal with the actual levels that were measured. Then finally to deal with the facts as they have been adduced before you as to how the drug was treated at the Hospital for Sick Children, the forms in which it was available, the manner of its storage and the circumstances limiting access to the drug, and finally the rules as to who might be in a position to administer the drug and under what circumstances.

Dealing then first, sir, with the general evidence that you have heard concerning the

drug and specifically its function and effect. I think I can with a great deal of confidence suggest to you, sir, there has been absolutely no disagreement on at least this issue amongst the experts, and that is the drug digoxin itself as a derivative of the Foxglove plant was known - its first recorded clinical use was known to have occurred in the late eighteenth century. You have heard extensive evidence on the drug from Dr. Mirkin, Dr. Spielberg, Dr. Kauffman, Dr. Hastreiter and others. Dr. Spielberg in particular has testified that the drug is in fact a reasonably old one, it has been used, in his opinion, with literally millions of patients with beneficial therapeutic effect. The pharmacologists who testified before you were in agreement, however, including Dr. Spielberg, that although the drug has that lengthy history both of use and identity to pharmacologists, there is an enormous amount about the drug that is yet to be discovered and fully defined, although much has been learned about the drug within the last three to four years that was not previously known or investigated in depth.

In chemical terms, Mr. Commissioner, Dr. Mirkin has described for you the basic composition of the drug. It is essentially as he described it a

3 steroid having three components. First a steroid nucleus found in all hormones in the human body. Secondly, a lactone ring. Thirdly, a chain of links comprised of sugar. The reason that is of interest, sir, in terms of a basic understanding as to how the drug works is because it is the similarity of the steroid nucleus found in digoxin to other compounds naturally occurring in the human body that makes it difficult to distinguish digoxin from other chemical compounds when various tests and techniques are applied.

In modern terms we have heard, sir, that digoxin is primarily used for the treatment of patients with congestive heart failure. It has two predominant functions. The first one, sir, is to improve the efficiency with which heart muscle, the myocardium, contracts so as to assist in the more effective circulation or pumping of blood by the heart throughout the entire body, that is its primary function. It has as well a number of secondary functions, as for example its effect on the conduction system of the heart and its use to treat disturbances of cardiac rhythym, that is the electrical activity of the heart.

As you know, sir, and you will forgive

me perhaps for restating the trite, the heart anatomically has four chambers, the left and right atrium and the left and right ventricals, the latter of which function essentially as the pumping stations of the heart.

To understand how the drug behaves we have heard from the pharmacologists that we have to understand what its effect is on the various chambers of the heart. Impulses arising in the atrium, or the atria chambers of the heart are carried through a network called the atrial ventricular node to the ventricals causing it to contract. Digoxin acts to increase the force of contraction in the ventricals and as well the rate of conduction of impulses from the atria to the ventricals. The latter effect can lead, according to Dr. Mirkin and Dr. Spielberg, to atrial ventricular dissociation, that is the independent beating of the ventrical at a very slow rate causing the heart in some instances to completely stop beating. If that occurs, sir --

THE COMMISSIONER: I am sorry, I am having trouble with that.

MS. CRONK: I will back up, sir. We have heard that the basic premise as to how the drug works is to increase the force of contractions that

take place in the ventricals of the heart.

THE COMMISSIONER: That's right.

MS. CRONK: And as well it operates to affect the rate of conduction of impulses which flow from the two atrium chambers to the ventricals, we have two effects then of the drug. If in fact the effect on the rate of conduction is pronounced it can lead to what has been described as atrial ventricular dissociation. You will recall that Dr. Mirkin in an attempt to express it in layman's terms suggested that the rate, the beating of the heart caused by the atrium can in fact be a different rate than occurs in the ventricals. If that happens the ventricals can start to beat independently at a very slow rate. That only happens if the conduction rate is affected by the drug, but if it does it can in extreme cases cause the heart to stop beating altogether. The pharmacologists have called that AV block or atrial ventricular dissociation, two different rates between two different types of chambers in the heart leading in extreme cases to the ultimate and slowing of the heart rate to AV block.

THE COMMISSIONER: Yes, I guess I understand that. You say digoxin - first of all on the pump, on the ventricals?

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MS. CRONK: That is right, sir.

THE COMMISSIONER: You say it increases their beating?

MS. CRONK: We have to distinguish between, as I understand the evidence, sir, we have to distinguish between two concepts; it operates first to improve the efficiency of contractions.

THE COMMISSIONER: Yes.

MS. CRONK: That is the effect on the pumping chambers and the ventricals that you have just spoken of.

THE COMMISSIONER: When you say improve the efficiency, you mean make it regular, steady?

MS. CRONK: That is correct, sir.

THE COMMISSIONER: Yes.

MS. CRONK: Then the second effect is actually on the heart rate itself on the conduction system, and it is particularly, for example, prescribed in situations where disturbances in cardiac rhythym have been diagnosed where there is an irregular rate, and it is intended that the drug operate on that to control the rate. I will explain that in physiologic terms in a moment, sir, but those are the two basic premises.

Perhaps it can best be explained this

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way. We have heard from the experts, sir, that in a patient with a failing heart, with congestive heart failure, the cardiac output of the patient is reduced. What that means effectively is that the amount of blood that is pumped out by the heart per beat is diminished. Digoxin by improving the efficiency of contractions of the heart increases cardiac output, it allows more blood to be pumped out per beat. In addition, however, and quite distinctly, it causes the heart to slow its rate in recognition of the increased blood flow. Dr. Mirkin has described this phenomena in this way. He said that when you have a situation where the cardiac output is diminished the body, the heart, tries to compensate in a natural way by increasing the rate of the heart, as the rate of the heart is increased obviously, sir, more blood is pumped. Where it naturally has a lower output the rate is increased naturally by the body. What digoxin seeks to do is to counteract that situation by increasing cardiac output and simultaneously slowing the rate to achieve a natural state of equilibrium. That was the evidence, sir, of Dr. Mirkin and I would refer you to Volume 4 at pages 505 to 507 of the evidence. That, sir, in principle is how the drug is intended to act and in fact is perceived to work.

8 In my submission, however, a general understanding of the pharmacokinetics of the drug are essential to an assessment of the significance to be attached to the concentrations of digoxin that have actually been measured in some of these children. Again the patterns of movement and behaviour of the drug have been outlined before you by a number of pharmacologists. I don't propose to deal with it in any detail but rather to refer you to certain portions of their evidence. They have advanced an explanation for the basic effects of the drug. They have told you, sir, that the primary desired effect of the drug, that is the improvement of the efficiency of contractions of the heart muscle is thought to occur as a result of the interaction of the drug with protein receptor sites located on the outer membrane of cardiac cells.

You may recall, sir, that Dr. Spielberg testified at length with respect to this phenomena. He has said in evidence that digoxin must bind to a particular protein receptor in order to have any pharmacological effect in the body whatsoever. In my submission, sir, this is a fundamentally important concept to understand how the drug works. The evidence from all the pharmacologists has been that

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so long as the digoxin is solely in the blood or serum of the human body it has absolutely no biological activity at all. In order to have any pharmacological effect, be it a therapeutic effect or a toxic effect, it must effectively reach the tissues of the body. Dr. Spielberg has said that these protein receptor sites and cardiac cells are known as sodium potassium ATP ase. Quite apart, sir, from the fact that it has taken approximately eleven months for some of us to pronounce that term correctly, I think the concept when examined is not a particularly difficult one.

Dr. Spielberg has said that these particular sodium potassium ATP ase are effectively, according to the current state of the medical art, enzymes that regulate the amount of sodium and potassium both inside and outside of cardiac cells. The state of the art suggests, according to Dr. Spielberg, that digoxin once administered affects the balance of the sodium and the potassium inside and outside of these cells such that calcium is allowed to enter the cell. It is his opinion, based on his experience and research in the area, that it is the entry of calcium into the cardiac cell that is thought to permit the functioning of digoxin to improve the pumping efficiency of the heart or contractions of the

heart.

So to restate it, sir, the primary effect of digoxin according to Drs. Spielberg and Mirkin is accomplished in that way, that is by the effect of the drug on the sodium potassium ATP ase enzymes on cardiac cells. A different chemical explanation however is advanced for the second affect of digoxin, that is its effect on the rate of conduction in the human body. According to Dr. Spielberg this effect on heart rhythym or heart rate is achieved from a very different kind of pharmacological activity. The vagus nerve we have heard, sir, originates in the brain and that it helps to control heart rate by virtue of its affect and what has been called the synoatrial node located in the atrium of the heart. Digoxin has a direct effect on the vagus nerve in the brain which in turn alters the rhythm of the heart by slowing the response rate of the ventricals to the faster rate of the atria.

In simpler language, Mr. Commissioner and perhaps this is the point where I should have started, Dr. Spielberg and Dr. Mirkin have described the functioning of digoxin in two ways. They have said that first it interacts specifically on cardiac

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cell receptors to increase the force of contractions in the heart.

Secondly, it acts on the vagus nerve in the brain to block or slow conduction having the result of slowing the heart rate.

We come then, sir, to the normal routes of administration of the drug and the pattern of behaviour of the drug depending on the route chosen. We know, sir, that the normal routes are intravenous or oral and intramuscular.

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E-1

The pattern of the behaviour of the drug varies enormously we have heard depending on two things: first, which route of administration is chosen, and secondly, the characteristics of the patient himself.

All of the pharmacologists who have testified before you are agreed that there are significant individual variability with the use of digoxin. And by that they have said that each individual will respond to the drug differently depending on that individual's clinical condition and chemical makeup, and that the potential for that degree of variability is very important in assessing the actual results, the concentrations that were measured in the 36 infants with which this Commission is concerned.

I propose to deal, sir, with the intravenous route of administration first.

Dr. Spielberg and Dr. Mirkin had testified that when digoxin is administered intravenously it first enters the serum or blood plasma resulting initially in extremely high concentrations of the drug in blood. Within several minutes, according to Dr. Spielberg, and within several seconds according to Dr. Mirkin the

level rapidly decreases and the drug enters a central compartment or volume of distribution.

From the central compartment it then distributes to the rest of the body; that is to the tissues. This entire process of distribution (that is the movement of the drug from the moment that it is administered through to its entry to the central compartment or volume of distribution and from there out in the body to the rest of the tissues and organs in the body) has been called the Alpha Phase. The time at which it reaches its final concentration or steady state is at the end of the Alpha Phase.

In effect, sir, the evidence demonstrates that the circulatory system of the body acts as a transport system for digoxin once it is administered. You will recall that Dr. Spielberg spent some considerable time explaining this phenomena, the pattern of the Alpha Phase, on a chart that was filed as Exhibit 217 (1), sir.

His evidence is that the time required for digoxin to distribute from its central compartment or volume of distribution to steady state (that is the end of the Alpha Phase) declines with a half life reported in the literature as

between 20 to 60 minutes. He estimated half life was 30 minutes.

The concept, Mr. Commissioner, of half lives associated with digoxin is again in my submission a most important one in understanding the pharmacokinetics of the drug. Effectively what this means according to Dr. Spielberg is that in each half life half of the drug which is in the central compartment or volume of distribution will leave that compartment and enter tissue.

It requires approximately 5 half lives or 2½ to 4 hours from the time of administration of the drug for it to achieve steady state or reasonably full distribution.

For example then, sir, you will remember in detail this evidence, that if - again assuming intravenous administration of the drug it takes either a few minutes or a few seconds to decline from its initially very high peak concentrations. Once it is then in the central compartment of distribution, if the level for example is 20, then the next half hour the level drops to 10.

THE COMMISSIONER: You are speaking of the central compartment; you are not speaking

of a place, are you?

MS. CRONK: No. The evidence has been, and I should have clarified that, although over several months that is how I thought about the concept. But the pharmacologists have indicated that it is really an abstract concept designed to pinpoint a point in time in the movement of the drug.

THE COMMISSIONER: It goes into the bloodstream and it leaves the bloodstream I take it at various places. During this Alpha Phase it leaves the bloodstream, some going to the heart -

MS. CRONK: Yes, that's correct.

THE COMMISSIONER: And some going to the brain and various other parts of the body.

MS. CRONK: That's correct, sir.

THE COMMISSIONER: At different rates.

MS. CRONK: That's right, sir.

EMT/ac

E.2.1.

THE COMMISSIONER: And the compartment, it is not a real -

MS. CRONK: It is certainly not a physical location within the body, sir. The concept as I understand it is one to indicate that there is a period of time after initial administration of the drug when the drug is still accumulated in the blood --

THE COMMISSIONER: Yes.

MS. CRONK: - when it is at a significantly high level. It then over the course of time distributes out in tissues.

Aside from whatever scientific interest there might be in this, sir, it is important to the interpretation of the levels of these children because if a sample is drawn at a time when the drug has not yet fully distributed, we have heard that it can result in very high falsely elevated readings.

THE COMMISSIONER: That is quite right. It is just this compartment I am still having some trouble with, but I take it really what is happening, it goes into the bloodstream and comes out of the bloodstream. It comes out, however, at a comparatively slow rate. It doesn't

E.2.2.

come out immediately. It comes out slowly and its one half life would be 30 minutes, but a whole life would be something like 2½ hours. And that is the time it takes to get out. Somewhere along the line you call this the compartment, or experts call it the compartment, do they?

MS. CRONK: To deal with it in the concept that you have advanced, sir, at the very start of the time when it begins to distribute to tissues we are dealing with the central compartment. But then as you have suggested it takes anywhere from 2½ to 4 hours to fully distribute to tissues.

The relevance or importance of this concept of half life is simply to recognize that the levels measurable in blood change dramatically depending at what point in time you have taken the sample. And if you have taken it before steady state or full distribution has been reached, the concensus amongst pharmacologists is you may get an extraordinarily high blood level which is easily subject to misinterpretation.

In addition, sir, we can't unfortunately leave the matter there because after the Alpha Phase we have to be concerned about something that pharmacologists have described as

E.2.3

Beta Phase, and what that is is the process whereby digoxin is eliminated from the body.

It appears, sir, according to the pharmacologists, that some digoxin in very minute quantities is in fact eliminated during the distribution or Alpha Phase, but predominently the elimination of the drug occurs after steady state has been reached.

We have heard that digoxin can only be excreted through the serum; that accordingly once steady state has been reached the digoxin that has been distributed to the tissues begins to re-enter the blood or the serum. It does so in one of two ways: it is either transported by the circulatory system to the kidneys where it is excreted, or alternatively it is metabolized or broken down in the liver. Those are the only modes of exit for the drug from the body regardless of the route of administration that was chosen.

THE COMMISSIONER: Metabolized through the?

MS. CRONK: Through the liver, sir. And by metabolization we have heard that the experts are referring simply to the breakdown or degradation of the molecules of the drug in a

particular organ; in this case the liver.

Once again, sir, we have to be concerned about the half life of the drug during the Beta Phase. That is how long does it take for the drug to be fully eliminated from the body?

Dr. Spielberg has testified that this amount of time is highly variable depending on chiefly three factors: the age of the patient, certain genetic and clinical differences such as the efficiency of the kidney whether there is any impaired renal failure - I'm sorry, any impairment to the kidneys - and thirdly, it depends on the rate at which the patient's liver metabolizes the drug.

He estimated that the half life of digoxin in the Beta Phase is anywhere from 20 to 80 hours, and that, sir, is one half life. Now it may vary enormously depending on the age of the patient.

THE COMMISSIONER: Did you say 20 to 80?

MS. CRONK: 20 to 80 hours for one half life.

Again it can be very different depending on the patient. His evidence before you is

that the total elimination of the drug from the body therefore takes 5 half lives or 5 times 20 to 80 hours. In the result total elimination would be achieved 5 to 20 days after intravenous administration depending on the characteristics of a particular patient. In any given case we have heard from both Dr. Mirkin and Drs. Kauffman and Spielberg it is very difficult to predict what half life rate in fact applied for that particular patient.

Assuming then that the drug has been distributed, fully distributed in the Alpha Phase and that this process of elimination has begun, the issue arises as to where we actually find it in the body if we look for it and begin to test for concentrations of it.

Dr. Spielberg has testified that certain organs or tissues take up the drug in greater prominence than others. In his list of descending order of prominence, sir, we will find the highest concentration of digoxin, again assuming intravenous administration, first in the heart; second in the kidney, third in the liver, fourth the skeletal muscle and fifth in the brain.

He suggested that even skin can

E.2.6.

disclose under certain circumstances significant concentrations of the drug. Dr. Mirkin essentially agreed with the list offered by Dr. Mirkin -

THE COMMISSIONER: Offered by?

MS. CRONK: By Dr. Spielberg, sorry, who placed the order slightly differently.

Dr. Mirkin suggested that the highest concentrations would be found first in the kidney, followed by the heart and then the liver.

The amount to be found in different tissues, sir, is dependent upon a number of factors. Again according to both pharmacologists we must be concerned with the age of a particular patient, the affinity of different tissues for the drug itself, the weight of the organ, the rate of the organ or tissue blood flow, the nutritional status of the patient, the patient's disease state, and the role of other medications or drugs.

Again, sir, apart from scientific interest the matter is of importance in interpretation of these levels for this reason: it is clear that depending upon the particular patient involved a sample taken for example from the heart tissue may yield much higher concentrations of the drug than

will a sample taken, for example, from the liver which Dr. Spielberg places lower down on the list, or a sample taken from the brain, again lower down on the list.

Again that may differ depending, if two different patients are involved, the concentrations measurable may be different according to the patient.

Dr. Spielberg has testified that a number of factors are relevant if we are going to try to extrapolate from a serum digoxin concentration the effect of the drug on tissues or vice versá. In other words, sir, if you have a measured concentration either in blood or in tissues can it scientifically reliably be said to represent what is in the other specimen type? He has said that the relationship between serum concentrations and tissue concentrations are age-dependent, the proposition being that there may be more digoxin receptors in infants than in adults.

What this means, sir, is that higher concentrations can be measured in infants than in adults. The reason that that has importance in interpreting these levels is that much of the reported literature which sets out or describes

toxic ranges of the drug are taken from case studies particular to adults; that it becomes difficult to extrapolate from literature that deals with toxic levels in adult serum samples to what a toxic level is in an infant.

Dr. Spielberg has also suggested it is conceivable that the protein receptors that he spoke about could become saturated, and if this were so he postulated the level of the drug in blood could be falsely elevated.

This concept of potential saturation of receptors was a contraversial one, sir, and I can tell you that you may recall in the evidence that other pharmacologists did not place as high a degree of confidence in the concept as it appeared did Dr. Spielberg. However, Dr. Spielberg himself acknowledged there was no hard scientific data which established one way or another whether or not receptors could become saturated. He simply felt it was a reasonable pharmacological proposition.

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I come then to the movement and behaviour of the drug, if the oral route of administration is utilized, as opposed to the intravenous route, sir. The importance here is that the distribution curve, the movement of the drug, itself, if it is administered orally is vastly different than if it is administered intravenously. You will recall, sir, we have heard from Dr.Mirkin that when digoxin is administered orally it enters the body through the esophagus, moves down into the intestines where it is absorbed and upon absorbtion is transported through specialized blood vessels back into the liver. A small portion of the drug, while it is in the liver, is metabolized or broken down, but the balance is then transported by the general blood circulatory system throughout the body to various other tissues and organs. It thus encounters, if you will, the liver first and moves from there out and distributes to other tissues and organs in the body.

According to Dr. Mirkin the result of oral administration is that the peak blood digoxin levels occur one to two hours after the drug is taken. Dr. Spielberg estimated that the peak occurred one to three hours after the drug was taken. This is of again a fundamental concept perhaps, sir, because it high-

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lights the enormous difference between the movement of the drug if it is administered intravenously and the movement of the drug if it is administered orally. You will recall that if it is intravenously the peak actually occurs within minutes, according to Dr. Spielberg, within seconds, according to Dr. Mirkin and when we come to oral administration in combination their evidence suggests that it is anywhere from one to three hours before those peak concentrations are reached.

In addition, concentrations which are measurable in blood at the peak level, if it has been administered orally, are approximately five times as great as are found at steady state, which is achieved approximately six to twelve hours later.

If you take a blood sample in that initial one to three hours after the drug has been administered orally you are going to get a level that is, according to Dr. Spielberg, likely five times as great as you will find at steady state when the drug has begun to distribute.

There are thus three major differences between oral administration and intravenous administration, Mr. Commissionor. First, the peak or maximum blood concentrations in the case of oral administration

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occur approximately one to three hours after the drug is taken, whereas if it is given intravenously it occurs immediately within minutes or seconds.

The second major difference is that the peak concentrations following an oral dose are lower than the peak concentrations following an intravenous dose.

Third, the drug tends to distribute amongst tissues following an oral dose in a pattern different from that observed following an intravenous administration. With a single dose given orally Dr. Mirkin has testified that high concentrations will be found first in the liver, which is, as you will recall, is the first organ the drug encounters on its distribution path, followed by the heart and followed by the kidney.

The next issue then, sir, is how the drug is used therapeutically in light of the given state of the art the given extent of scientific knowledge as to how it works in the body.

The evidence before you has established, sir, that patients of different age groups have varying degrees of senitivity to the drug. Dr. Mirkin has testified that in light of the importance of the age factor infants generally receive digoxin in twice the

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doses per unit of weight as do adults. That does not mean, sir, that the total volume given to an infant is twice the total amount given to an adult. It simply means that when measured, according to the body weight of the infant, it is proportionately higher.

The pharmacologists and the cardiologists who testified for you, have agreed that the drug has what they call a low therapeutic index. What that means, sir, as I understand their evidence, is that the concentration of the drug which produces toxicity and in some cases fatality, does not greatly exceed the concentration that will produce a desirable therapeutic effect.

While there are recognized symptoms of digoxin toxicity, the cardiologist and pharmacologist, who testified before you, agreed unanimously that there are no symptoms diagnostically indicative of or specific to digoxin. In other words, while there are symptoms which are suggestive of digoxin intoxication, and can be regarded clinically as such, they may, in fact, be due to a myriad of other causes. I refer specifically, sir, to the lengthly evidence given by Dr. Rowe on this matter, which is found at Volume 19, commencing at page 3325.

Dr. Rowe listed for us the various

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clinical symptoms which he felt were suggestive of digoxin toxicity. They included, first, heart block or AV Dissociation Second, arrhythmias, such as ventricular fibrillation, a very fast heart rate. Third, rhythm disturbances detectable by electrocardiogram changes. Forth, persistent vomiting and nausea. Fifth, bradycardia, a slow heart rate. Sixth, sudden terminal events. Seven, shallow respirations.

Dr. Mirkin, sir, essentially agreed with the symptoms that had been outlined by Dr. Rowe and added others that were particular in the case of adults which we need not be concerned. Dr. Spielberg agreed, particularly, that nausea and vomiting, bradycardia and arrhythmias which he calls dysrhythmias are manifestations of digoxin toxicity, although non-specific. Dr. Spielberg added to the list, as the eighth factor, low serum potassium and increased calcium levels.

There was, as you may recall, sir, a certain amount of disagreement amongst the experts as to whether or not convulsions or seizure -like activity observed in infants was a symptoms of digoxin toxicity. Some felt that they were, some felt that it was not and it is certainly true, sir, on the evidence that in a large number of these children

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seizure-like activity of one degree or another was observed clinically prior to their death, and, indeed, as part of the agonal or terminal events. There are, as well, sir, certain situations where the drug is contra-indicated in situations where the experts have said a particular infant may be pre-disposed or more sensitive to digoxin toxicity than others. The circumstances, sir, are, in my submission, important to an understanding again of the levels that were measured in these children because it may well be that certain of these children had conditions which pre-disposed them to digoxin toxicity, such that a lower amount of the drug would cause toxicity than would otherwise be expected or required.

Dr. Mirkin, for example, indicated that where a patient is suffering from ventricular tachycardia it was a clear case where the drug should not be used. It was contra-indicated in that case.

In situations where there are significant electrolyte imbalances, and by that, low potassium levels or high calcium levels, the drug should be used with caution. Again, because in some patients depending on their age and their condition, they can be sensitive, made more sensitive to the drug, because of their electrolyte imbalance than would otherwise

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be the case.

Thirdly, if there are abnormalities in the endocrine system the patient maybe more disposed to digoxin toxicity than would otherwise be the case.

Fourth, situations where a patient has an intrinsic heart dysrhythmia prior to the administration of any medication, that is if there is an inherent history of arrhythmias, without the introduction of any medication .

Then fifth, suggested --

THE COMMISSIONER: Just a minute before you go on. What is the purpose of digoxin if it is not to correct these arrhythmias?

MS. CRONK: Sir, clearly from what the pharmacologists have said, it can have a very desirable theraputic effect. The thrust of their evidence is that it has to be used with caution. In a therepeutic context a very close monitoring must be kept of the reaction of a particular patient to the amount of the drug that has been given. That is because, for example, if there is a prior history of arrhythmias a smaller amount of the drug may produce toxicity than would otherwise be expected.

You will recall, sir, that we heard at length from Dr. Ellis and Dr. Soldin, as to what

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the objectives are, of the use of digoxin and its measurement in a clinical or hospital setting, the purpose is to achieve a balance between the desired therapeutic effect, at the same time, avoiding any possibility of toxicity.

These are really situations, sir, where the pharmacologists, as distinct from the clinicians have said that patients may react more adversely to the drug than otherwise if the wrong amount of the drug is given at a particular stage in the client's course in the Hospital.

Sir, I am about to move to another area. Do you want to take a break at this time?

THE COMMISSIONER: Yes, 20 minutes.

--- Recess at 11:10 a.m.

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---On resuming.

THE COMMISSIONER: Yes, Miss Cronk.

MS. CRONK: Thank you, sir. Sir, I propose next to deal with the evidence of various witnesses concerning what is or is not an accepted therapeutic range of digoxin level in an infant, and similarly what is or is not a recognized toxic range for a digoxin level, again in an infant.

The evidence before you in this regard, dealing first with Dr. Ellis and the Residents Handbook of Paediatrics published at the Hospital for Sick Children in 1979. Dr. Ellis indicated that in the handbook the levels are described thus: Under 0.5 nanograms per millilitre is indicated to be indicative of under digitalization. 0.5 to 2.5 nanograms per millilitre is expressed as being optimal, that is therapeutic. 2.5 to 3.0 nanograms per millilitre is expressed as being the overlap area. Greater than 3.0 nanograms per millilitre is expressed as being over digitalized or toxic.

Dr. Ellis testified that during the enquiry period, that is July 1980 through to the end of March 1981, those were the guidelines that applied at the Hospital for Sick Children, and as a

result any level of greater than 2.5 was technically to be considered in the toxic range, or at least in the overlap range potentially toxic. He did however, indicate that the guidelines as set out in the handbook were derived from research studies particular to adults and not infants, and accordingly there was a footnote to that particular section of the handbook which drew to the attention of those who would be using and relying on that handbook that infants could in fact tolerate higher levels than were recorded in the handbook. That is found, sir, at page 365 of Exhibit 16 the handbook which has been filed.

There is a consensus among all witnesses, Mr. Commissioner, as I alluded to earlier, that infants can in fact tolerate higher concentrations of digoxin than do adults.

The evidence of the pharmacologists as to what is or is not an accepted therapeutic range differ slightly from the evidence of the cardiologists on the same issue.

Dealing first with the cardiologists, we heard from Dr. Rowe that although the guidelines in the Residents Handbook indicate a therapeutic or optimal range of .5 to 2.5 nanograms per millilitre, children can in fact have much higher blood concentrations

without experiencing any toxic effect at all. Those were situations where the baby was healthy, there were no manifestations clinically of toxicity and the baby survived.

He testified however that a level of 10 nanograms in his opinion, in an infant, was at least twice the maximum therapeutic range. A level of 3.5 nanograms would cause him as an experienced cardiologist to withhold further digoxin and to watch the child fairly closely to see if clinical symptoms of toxicity were in fact manifested.

Dr. Fowler testified that his impression during the relevant nine month period was that a therapeutic level was below 2 nanograms per millilitre for an infant, although a patient could experience a level as high as 4, again without manifesting symptoms.

Dr. Freedom put the therapeutic range as between 1 to 3 nanograms per millilitre. Dr. Bain not a cardiologist but a very eminent and experienced paediatrician testified that the desired therapeutic level was somewhere under 2 or 3 nanograms although a level of up to 3.5 was acceptable.

Dr. Hastreiter at the Preliminary Hearing involving Susan Nelles testified that for premature or new born babies the cut-off point was 4.5

nanograms. For babies aged 3 to 12 months the cut-off was 3.5. Once an infant became a year of age or older the level reverted to that applicable for adults
4 and the cut-off became 2.5. That was his evidence that premature infants or neonates could tolerate a higher range 4.5 and it went down in descending order according to the age of the child.

Amongst the clinicians, sir, in an effort to summarize what the evidence has been, the highest level mentioned as being within the therapeutic range was that of Dr. Hastreiter for neonates a level of 4.5. The majority of the cardiologists at the Hospital for Sick Children placed it between 2 and 3.5, beyond that any level would be of concern. The pharmacologists and biochemists as I have suggested dealt with it slightly differently. Mr. Cimbura suggested that as a general guideline a level of up to 3 to 4 in a pre-mortem plasma sample is what he would have regarded as within a therapeutic range.

Dr. Mirkin indicated that in young children or infants a level of 2.5 nanograms would be the cut-off point, that is the upper therapeutic limit, although it would not be unusual for infants again to have levels of 4 or 5 without exhibiting signs of toxicity. On balance then he suggested that

the range for infants today would be considered properly to be between 2.5 and 5 nanograms per millilitre.

Dr. Speilberg suggested that the level for adults was as stated in the handbook, that is between .5 and 2.5 nanograms and didn't define how much high he felt would be a therapeutic range for infants.

Dr. Kauffman put the level for infants between .8 and 3 nanograms. Dr. MacLeod suggested that higher concentrations of 3 or 4 could be tolerated in infants. Dr. Soldin put it between .8 and 2 with an overlap area of between 2 and 3. Amongst the pharmacologists and biochemists then, sir, the highest therapeutic level mentioned was that referred to by Dr. Mirkin for infants .5 nanograms. The majority of the --

THE COMMISSIONER: I am sorry.

MS. CRONK: I'm sorry, sir, 5 nanograms, not .5, 5 nanograms, that was the highest mentioned.

THE COMMISSIONER: Dr. Mirkin did you say?

MS. CRONK: By Dr. Mirkin for infants. He suggested you will recall that the range was between 2.5 and 5.

THE COMMISSIONER: Yes.

MS. CRONK: The majority of the pharmacologists place the maximum range as somewhere between 2 and 3 nanograms, that is Drs. Kauffman, MacLeod, Speilberg and Soldin.

In my submission then assessing what has been said both by the cardiologists and the pharmacologists leaving aside premature neonates, the general therapeutic range for infants may be stated as somewhere between 2 and 3 or 3.5 recognizing two features, that higher levels can be experienced by children without any manifestation clinically of symptoms of toxicity; and secondly, given the variability that depends on the age of the patient, symptoms can be manifested with concentrations even lower than the range of 2 to 3 or 3.5.

We come then, sir, to the issue of how one goes about testing to determine what the actual level or concentration of digoxin in fact is in a particular patient. You have heard from a number of witnesses as to the analytical techniques that are available for these purposes. Mr. Cimbura has testified that there are a number of general problems quite apart from the particular technique or assay used that render the testing of digoxin extremely difficult. He said two things in this regard; the

7 quantities of the drug available in the body for detection are extremely small. This necessitates the measurement of the drug in nanograms per millilitre. You will recall, sir, that 1 nanogram is one billionth of a gram.

He said secondly that digoxin has a high molecular weight in chemical terms and that it therefore does not render itself to testing on various analytical techniques that were primarily designed to test chemicals of a lower molecular weight.

As a result of both of those two factors he suggested, there was no disagreement on this from other experts, that whatever technique is in fact employed it must of necessity be extraordinarily sensitive to actually measure levels of concentrations of digoxin.

Generally, sir, you have heard that there are five techniques currently available in the scientific community for the measurement of digoxin. The first is the radioimmunoassay or RIA technique. The second is a technique more recently adopted in a hospital setting known as the fluorescent polarization immunoassay or FPIA technique. The third is high pressure liquid chromotography or the HPLC technique.

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The fourth is mass spectometry coupled with gas liquid chromotography; and the fifth is a combination of any of the preceding four.

It is not, sir, my intention to review in detail the mechanics of how these various assays work, but it is in my submission relevant to you to know what the pharmacologists have said as to the reliability of each of the techniques, such that some, in the opinion of some of the experts you have heard from, are more reliable in actually detecting the presence of digoxin and the concentrations of the drug that are in fact present.

Dealing first with the RIA or radio-immunoassay technique; in general terms, sir, you have heard it involves a competition if you will between a sample of digoxin that has been treated radioactively, a competition between that sample and a patient's sample of interest which may or may not contain digoxin of course, and the two compete for a binding site on an antibody. That relates, sir, to the pharmacological concept explained by Dr. Speilberg that digoxin reacts with protein receptor sites on the cell membrane of cardiac cells. There are therefore receptor or binding sites which will take up or absorb digoxin on those cells. The radioactively

treated digoxin competes with the patient's sample for those sites on the cells. By use of a separation technique the digoxin that has become bound to those antibodies is separated from the digoxin which has not become bound, that is still free floating in the mixture. The bound digoxin is then transferred to a machine, a gamma counter which measures the radio-activity present in the mixture on the antibodies.

A computer process is then used to compare the amount of radioactivity present in the sample to the amount of untreated or non-radioactively treated digoxin so that by a deduction process the computer can tell you how much digoxin was present in the patient's sample because none of it was treated radioactively.

You will recall, sir, that Dr. Ellis was good enough in his evidence to explain at length how this procedure works, and a diagram was filed as Exhibit 22 which attempted to illustrate in a step by step fashin how the IRA assay that is employed at the Hospital for Sick Children works.

A matter of importance, Mr. Commissioner, is to the interpretation of results obtained on RIA assay is the fact that drugs or compounds having a molecular structure similar to digoxin can cross react on the RIA antibodies.

That is they are able to bind with the antibody used in the process just as digoxin is. As a result many experts have testified before you that a digoxin level recorded by use of the RIA method may be a level reflecting not only digoxin but digoxin-like substances.

I will turn in due course, sir, to the evidence that you have heard chiefly from Dr. Seccombe of Vancouver and others concerning what has been called Substance X. But leaving that aside for the moment, substances that have been identified as potentially cross-reacting on the RIA assay are, first, metabolites of digoxin (that is the breakdown products of digoxin itself), and secondly, separate and discrete drugs which are chemically similar to digoxin. An example of one of those given by Mr. Cimbura was digitoxin.

Basically, sir, you will recall the evidence of these experts that the various manufacturers of the RIA kits have through experience and reported cases in the literature identified known drugs which cross-react on the assay, and for that purpose where the drugs are known they have fashioned and designed an antibody which will not attract the known drugs that react chemically similar

to digoxin.

The issue, of course, arises whether or not any particular antibody has been more or less refined to exclude the possibility of cross-reaction by known drugs.

The third catagory of potential cross-reactivity is, of course, Substance X. As I have indicated, sir, I will have submissions to make with respect to it in a few moments.

It is this problem of the potential for cross-reactivity of the antibodies that are used in the RIA assay, sir, that gives rise to the question of whether or not digoxin or digoxin-like substances are produced naturally endogenously in the body. That is the Substance X issue.

The next technique available, sir, the FPIA method is a technique that is essentially similar to the RIA technique. It involves a similar competition process between a sample containing a known amount of digoxin that has been chemically treated with a patient sample that may or may not contain digoxin. Again, a competition for a binding site on an antibody.

Both techniques utilize standards and controls containing a known amount of digoxin.

Both utilize a specific antibody produced and made available by commercial manufacturers, and both are designed to run assays only on serum or plasma samples.

The primary distinction arises from the feature that with the FPIA technique radioactivity is not used to spike, if you will or treat the control samples, but rather fluorescein is used.

The second distinguishing feature is that there is no separation process utilized under the FPIA technique although there is under the RIA. The operative process of the FPIA technique, Mr. Commissioner, has been outlined for you by Dr. Soldin of the Hospital for Sick Children who is currently in charge of the therapeutic drug monitoring program at the Hospital and who has had personal experience in using this new technique for the purposes of digoxin assays.

He has explained the technique essentially involves a shining of a polarized light through the mixture being tested. The mixture includes both the patient sample and the sample containing a known amount of digoxin treated with fluorescein.

The degree to which the fluorescein labelled digoxin becomes bound to the antibody is reflected in the type of light that is emitted at the other end. If a strong light is emitted it indicates binding by the fluorescein labelled sample, whereas if a weak light or weak signal is emitted, it indicates that the patient sample has become bound.

The FPIA process was not in use at the Hospital for Sick Children during the enquiry period for digoxin assays, Mr. Commissioner. It was not introduced for digoxin assays until March, 1983, and since that time the Hospital has been utilizing both the RIA and the FPIA techniques for their digoxin assays.

As a result none of the measured digoxin concentrations with which you are concerned were measured utilizing the FPIA technique.

Dr. Soldin testified concerning certain comparative studies that had been run at the Hospital for Sick Children as an aid to determine whether or not the FPIA system should be adopted at the Hospital. It was his opinion that the results of these various studies suggested that the FPIA method may be more specific than the RIA in the sense that the antibody may diminish the potential for

cross-reactivity more than the antibody used in the RIA system.

In my submission, Mr. Commissioner, whether or not this is so, as relevant as it may be for the purposes of the Hospital, it is irrelevant for your purposes for two reasons: first, Dr. Soldin has testified that had the FPIA technique been available at the Hospital during the enquiry, and had it been used instead of the RIA to measure the ante mortem and post mortem blood specimens that were tested, he would not have expected any material difference in the readings obtained, but rather would have anticipated that the results would have been fairly similar.

Of equal importance, sir, is the fact - this is the second basis for my submission to you - the fact that the FPIA technique, like the RIA, is an antibody based system or analytical technique. The antibodies obtained by commercial manufacturers therefore too suffers from the potential of cross-reactivity by drugs chemically similar to digoxin or by digoxin-like substances whether those be metabolites or otherwise.

Dr. Soldin's evidence in that regard, sir, is found in volume 9, page 1517 to 1518.

In my submission for those two reasons it cannot be argued as between the RIA and the FPIA technique that the digoxin readings obtained on these children are suspect or unreliable in any way.

THE COMMISSIONER: The main reason for the change was the speed, was it?

MS. CRONK: The speed and the convenience, that's correct. That is Dr. Soldin's evidence. And in fairness to Dr. Soldin it is his opinion that it may ultimately prove that the FPIA is more specific.

THE COMMISSIONER: But the main reason - this is my recollection - was the speed.

MS. CRONK: Was the speed. That was his evidence.

The third technique, sir, about which in my submission we have to pay more particular regard is the HPLC method. That technique has been described by Mr. Cimbura as a test which permits the prior refining of a sample so as to extract from it digoxin-like substances.

It is intended, he testified, that the sample so refined freed in his opinion of digoxin-like substances would then be re-analyzed using

another testing technique as, for example, the RIA.

Mr. Cimbura detailed in his testimony the actual methodology involved in using an HPLC technique. He described it essentially as an extraction or separation process. He indicated that the equipment consists of a column containing special absorbant material. A standard sample containing a known amount of digoxin is run through the equipment (that is driven through the column) and its component chemicals are separated by virtue of this absorbant material in the column.

Each component exits the column, actually leaves the equipment, at a different point in time. The time at which each component exits the column is characteristic of a specific compound. In other words, using a standard sample which contains a known amount of digoxin, the time at which digoxin will exit the column can be precisely defined.

The sample of interest, the one about which it is uncertain whether or not it contains digoxin is then driven through the column in the same way, and if it exits the column at the same time as digoxin is known to exit, it is retained for further testing, and in Mr. Cimbura's laboratory was then subjected again to the RIA for further assay.

An important feature of this particular technique, Mr. Commissioner, again in my submission of more than mere scientific interest with all due respect to the scientists who testified before you, is that HPLC in and of itself is not capable of measuring the concentration of digoxin present. Its purpose is to try to extract or isolate the digoxin in the sample, the concentration of which is then to be measured by another technique.

The measurement of the concentration if done by what is called a detection type technique. The RIA is simply one of those that is available for detection purposes. The fourth and final pure method or analytical technique about which you have heard evidence, sir, is gas chromotography and mass spectrometry. You have heard evidence as you will recall, sir, that Mr. Cimbura indicated that because of the high molecular weight of digoxin, some techniques are not readily applicable or available for the testing of digoxin concentrations.

That was his view and expressed opinion with respect to gas chromotography and mass spectrometry because they were, according to his evidence, designed primarily for testing substances having a lower molecular weight.

The process of mass spectrometry itself involves subjecting the sample of interest to what has been described as a bombardment, if you will, by a stream of electrons with the intent of dividing the molecule or fragmenting it into particles. The fragments or particles are then analyzed again by hardware, by equipment, to identify what the molecule in fact was. And the way this is done, sir, is that each chemical fragment that has been separated by the use and application of the electrons carries with it in chemical terms a characteristic distinctive of the molecule from which it came. Also in chemical terms carries with it the pattern of chemical activity that is characteristic of the parent molecule.

The equipment used in the process then produces a printout or a chart which depicts the peaks of activity or the characteristics of the fragments tested. The characteristics of digoxin are known in the scientific community, and a reading of the charts produced by use of mass spectrometry are then analyzed to determine whether or not any of those fragments showed the activity characteristic of digoxin or demonstrated the characteristic distinctive of the digoxin molecule itself.

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The importance of this technique, Mr. Commissioner, arises from the fact that Mr. Cimbura used it at the Centre of Forensic Sciences in three situations, for the testing of some of the samples from these 36 children. I will return to that in more detail, sir, but he used it on certain specimens from Stephanie Lombardo and certain specimens from Jessie Belanger and on a fixative solution which was used to preserve heart tissues from Colleen Warner. It was not used on more samples according to Mr. Cimbura for a number of reasons. He described the reasons as being reflective of the inherent disadvantages of the technique. They were first, as I have indicated, that it is designed and applicable in the first instance to molecules having a lower molecular weight than digoxin.

Secondly, although it is a very sophisticated technique, it is extraordinarily time-consuming and concomitantly expensive and thirdly, in an analytical sense it requires extensive purification of the sample before any testing can be done at all.

To this might be added for reasons that were outlined by Mr. Cimbura he had, in any event, sir, concluded on the basis of research conducted in

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his laboratory, that he had been able to fashion and design another method that was capable of, in fact, isolating pure digoxin and, in fact, capable of measuring the actual concentration of digoxin. I will have more to say about that combination in due course. You will recall, sir, that it was RIA followed by HPLC and RIA again.

The reliability of the results achieved on these various samples, sir, is, in part, a measure for the reasons that I have outlined of the reliability of the technique itself, that was used. Apart from the potential for cross-reactivity by digoxin metabolites and known drugs that are chemically similiar to digoxin there is, of course, the potential as well, that there is an existence of an endogenous digoxin-like substance which, in some cases, can cross-react to the antibodies used in commercial RIA digoxin assay tests. If that is the case the literature suggests that a so-called false positive reading of digoxin may result, that is, a finding of digoxin where the patients tested have not, in fact, received the drug.

Numerous articles have been filed as exhibits before you, sir, reflecting the current state of the art in the scientific community, as to whether

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or not such an endogenous-like substance, in fact, exists. It has been referred to in these proceedings by Dr. Seccombe and after Dr. Seccombe by everyone else, as substance X. There is a debate amongst the experts, as to what, in fact, the substance is. It has been variously described as first a natriuretic hormone, which promotes excretion of sodium by the kidneys. That was Dr. Seccombe's feeling and Dr. Hastreiter's feeling. Alternatively it might be a substance, in fact, manufactured endogenously in the liver, such that it might be prevalent in situations where there is liver disease and, thirdly, it was suggested by Dr. Hastreiter that it might be a progesterone derivative. Whatever the substance in fact is, Mr. Commissioner, you have heard direct evidence from a number of witnesses that it, in fact, appears to exist. In principle, you have heard, quite apart from the articles reported in the literature, that have been filed as exhibits, you have heard direct evidence as to six studies that have been conducted in the area. You have heard from Dr. Seccombe as I have said, from Shaughnessy Hospital in Vancouver, concerning the results of research reported by him in a letter to the editor of the New England Journal of Medicine in April of 1983.

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Second, you have heard from Dr. Soldin, concerning digoxin assays and the results therefrom run on children from Ward 7F at the Hospital for Sick Children in January 1982. You will recall that was the situation, sir, involving epinephrine and confusion with a vitamin.

You have heard from Dr. Soldin, thirdly, concerning digoxin assays run on eight children from Ward 7G in 1982 and 1983 at the Hospital, those children known not to have received digoxin.

Fourthly, you have heard from Dr. Soldin concerning certain ongoing water loading experiments which he is conducting in an effort to isolate substance X.

Fifth, you have heard from Dr. Phillips of the Hospital for Sick Children. You will recall sir, that he is Chief Pathologist at the Hospital concerning post mortem digoxin assays which have been conducted at the Hospital for Sick Children since the end of the inquiry period, that is, since March 24 1981, and finally you have heard from Mr. Cimbura concerning a study which he undertook in an effort to duplicate the results that had been reported by Dr. Seccombe.

The purpose, my purpose, sir, in

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outlining for you the evidence with respect to these various studies, is to assist, if possible, sir, you in assessing the evidence which you have heard from Mr. Cimbura that the technique used by him at the Centre of Forensic Sciences can and, in fact, does in his opinion, and I should say in the opinion of others, reliably isolate digoxin and reliably measure the concentrations of digoxin present in a patient specimen without concern that substance X may be reacting in such a way as to account for the levels that were measured.

It I could deal first, sir, with Dr. Seccombe's research. Dr. Seccombe testified that he and his colleagues tested serum and cord blood specimens from 25 randomly selected premature infants in the Intensive Care Unit of his Hospital, none of whom had been given digoxin. Their ages ranged from one to 146 days of age. The samples were assayed in duplicate using two different RIA procedures. The first was precribed by him as the NML methodology which is a particular antibody kit and, secondly, using clinical assays more common in the commerical market. The results in 10 of these 25 cases were reported by Dr. Seccombe and his colleagues in a letter to the editor of the New England Journal of Medicine which

has been filed, sir, as Exhibit 8. He has testified that the results from these 10 cases, using first the NML antibody assay ranged from a low of .8 nanograms per millilitre to a high of 4.1 nanograms per millilitre, the latter the highest reading was in the case of a four day old premature female infant. The results on the samples that were tested, using the RIA procedure were, according to Dr. Seccombe, 50 per cent lower in all cases. All of the results, save for the level of 4.1 nanograms, fell, as he admitted, within the commonly accepted therapeutic range for digoxin, but none of these children had, in fact, received digoxin. His evidence, sir, in this regard is found at Volume 5, commencing at page 631 and continuing.

Dr. Seccombe testified, sir, that his research group was quite confident that the substance that they were measuring was not, in fact, digoxin, but rather a substance reacting to the antibody in a fashion similiar to digoxin. Accordingly, they undertook a series of subsequent studies to enlarge upon the matter. They tested a group of 30 samples using 7 different RIA methodologies. They found that every kit, that is all 7, showed some degree of cross-reactivity with substance X, meaning that they

got positive readings, although samples had all come from infants known not to have received the drug.

The mean values of substance X on those tests ranged from 1.3 to as low as .19.

Dr. Seccombe made the following observations based on his research which, in my submission, are relevant to you, sir. First, that the levels of substance X declined to less than .2 nanograms per millilitre after two months of age in full term babies. In other words, the level of substance X that is measurable declines as the child ages. Second, levels greater than .2 nanograms were recorded only in premature infants.

THE COMMISSIONER: I am sorry, greater than two?

MS. CRONK: Greater than .2, sir.

THE COMMISSIONER: Yes.

MS. CRONK: Were recorded only in premature infants either in the neonate category. By that he meant less than two months of age or in some premature infants, slightly older than two months.

Third, he indicated that none of the tests which had been conducted by his research group, had been done using an HPLC extraction method

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nor had any other research in this area concerning substance X, to his knowledge, been done using HPLC.

Fourth, none of the levels recorded in similiar research reported in the literature exceeded 4.1 nanograms.

The significance of those observations, Mr. Commissioner, in my submission, is this: Dr. Seccombe modestly was invited to confirm that his research group was effectively on the threshold of a new scientific frontier in their research in this area. The level of 4.1 nanograms, which was measurable on their tests was, he has confirmed, the highest yet to be recorded by any research group concerning substance X. That level was found in a premature infant less than two months of age.

If I could turn now to Dr. Soldin's research and, first, the research that was conducted on Ward 7F, the Hospital for Sick Children in January of 1982. When I say Dr. Soldin's research, in fairness, Mr. Commissioner, the evidence was led through Dr. Soldin. I do not mean to imply that he personally was involved in the testing of all these samples, although, of course, he may well have been.

Out of a total ward population of 15 children, 5 became ill with similar symptoms.

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Only one of these children was on digoxin therapy, one out of a total of 15. All of the 15 were under 16 months of age, most of them under two months of age. Samples were taken ante mortem serum or plasma, save for those from one child out of the 15 who was known to have cardiac problems. Digoxin assays were run on all the samples using the RIA technique at the Hospital. The results were as follows: first, in the 10 cases of the children who had not shared in the similarity of clinical symptoms, no level was reported greater than .5 nanograms. Secondly, in the other 5 cases where there was this similarity of clinical symptoms, all levels reported were less than one nanogram except for two cases, the one patient who had been on digoxin therapy was the first exception. His levels were 2.1 and 1.4 nanograms and one other patient who had two levels of 1.3 nanograms each. In other words, sir, two levels of 1.3 nanograms were recorded in a child known not to have been on digoxin insofar as the Hospital was concerned.

There is a dispute on the evidence before you, sir, however, as to the circumstances surrounding that case where the level of 1.3 was found.

Mr. Justice Dubin reported that this

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level resulted from an erroneous administration of digoxin. That is found, sir, in the report of the Dubin Review Committee, page 178. Dr. Soldin and Spielberg, however, testified --

THE COMMISSIONER: I am sorry, I wonder if you could just pause for a moment on that.

MS. CRONK: Page 178, sir.

THE COMMISSIONER: Yes, all right.

MS. CRONK: You will see, sir, that was the reported finding based on information no doubt that had been provided to the Committee, of the Review Committee, as to how that level, what the circumstances were concerning that level of 1.3. They suggested, in fact, digoxin by error, had been administered to the child. Obviously, sir, if that be so, a measurement on the technique used at the Hospital is not surprising.

Dr. Soldin and Spielberg however, testified that they were uncertain as to whether or not this, in fact, had occurred and that the level if it hadn't occurred, the level might, in fact, reflect the measurement of substance X.

Assuming that the level of 1.3, making that assumption for the moment, sir, resulted in a case where there had been no medication error, the

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level measured is within the range of results previously measured -- I am sorry, previously discussed by Dr. Seccombe's group. In other words, it doesn't exceed the highest level of 4.1 that his group measured.

The second data base, if you will, that Dr. Soldin outlined for you on this issue, involved tests, digoxin assays that had been conducted on eight patients from Ward 7G again at the Hospital for Sick Children. In 1982 ante mortem plasma and serum samples were taken from three neonates on Ward 7G at the Hospital and were assayed for digoxin.

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None of the three had been on digoxin, and all three readings on the RIA were less than .5 nanograms per millilitre.

In the following year, 1983, ante mortem, again serum or plasma samples were tested from eight neonates, and by that I should say, sir, that Dr. Soldin explained he meant children under two months of age. Samples from eight neonates known not to be on digoxin were again assayed. Five samples were tested on RIA and by this time the FPIA technique was available in the Hospital and accordingly all eight samples were then as well tested by the FPIA method, and only one reading was above 1 nanogram on either type of assay test and that reading was 1.4 recorded on RIA. Accordingly all of the levels reported from those in total 11 children were first within the therapeutic range but much more importantly, because the children had not been on digoxin, were within the range of levels reported by Dr. Seccombe's research group.

THE COMMISSIONER: 11 did you say?

MS. CRONK: There were three children tested in 1982.

THE COMMISSIONER: Yes.

MS. CRONK: Eight in 1983, all from Ward 7G, all neonates.

THE COMMISSIONER: Yes.

MS. CRONK: The third area of independent research about which Dr. Soldin has given evidence, sir, is that involving what he described as water loading experiments. You will recall perhaps, sir, that he testified that ante mortem serum samples and urine samples had been tested by him, together with his colleagues, for digoxin from 12 or 13 adults in his laboratory in the Biochemistry Department at the Hospital. None of those adults had either current or past renal or cardiac problems and no history of having ever taken digoxin.

Dr. Soldin's evidence in this regard, sir, is found in Volume 51 commencing at page 1488. The tests were conducted on these specimens utilizing, according to Dr. Soldin, the RIA technique, the HPLC technique and the newer FPIA technique. The tests disclosed that substance X could not be measured under conditions of a water load in the serum samples of these individuals. It was however detected in the urine specimens. By that, sir, as I understood his evidence, what he meant was that a positive reading was obtained using those techniques on the urine specimens, whereas a negative reading if you will was obtained on the blood or serum specimens. Dr. Soldin

confirmed in his evidence that as at the date he testified he had not been able to quantify the levels of substance X that in fact had been measured on the urine specimens, he had simply been able to confirm its existence.

In other words, sir, in a quantitative sense he could not offer us any information as to the range of values that in fact had been measured. He indicated further that he had not at that stage undertaken tests to attempt to isolate substance X in tissues, although he hoped that the opportunity would be provided to him to do so.

Subsequent to the evidence of Dr. Soldin in this regard, enquiries were made by Commission Counsel from time to time as to the status of Dr. Soldin's ongoing research and I would refer you, sir, to Exhibit 418 which counsel for the Hospital, Mr. Roland, was kind enough to provide and which has been filed as an exhibit before you. It is dated, sir, May 15, 1984, and in that letter Mr. Roland on behalf of the Hospital has advised that Dr. Soldin's research is continuing but that, and then I am quoting, sir:

> "Until the research has been completed and the results have been properly and

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"independently assessed it would not..."

In their opinion be helpful or appropriate to entertain any additional evidence from Dr. Soldin.

In my submission, sir, as the matter now stands, the following is the result. First, we do not know what the actual measurements were on the urine specimens tested by Dr. Soldin's group. We do know they were from adults not infants, and we do know that no tests have been done on tissues.

The second feature is we therefore cannot determine whether or not the actual quantitative measurements are significant in terms of Dr. Seccombe's research or not.

Third, as the matter now stands, Mr. Commissioner, Dr. Soldin is not in a position to assist this Commission or to add anything further to his prior evidence regarding these experiments.

If I can turn then, sir, to the last area of research data that according to the evidence before you is available at the Hospital for Sick Children. It concerns the research being conducted under the supervision of Dr. Phillips of the Pathology Department. You will recall, sir, that the evidence before you has been that since March 24th, 1981 post

mortem digoxin assays wherever possible had been taken on all patients who died at the Hospital for Sick Children. Dr. Phillips has testified that since March 24th, 1981 in 608 autopsy cases digoxin levels were obtained at the Hospital for Sick Children on post mortem blood samples. I refer you for that, sir, to Exhibit 230 in this regard and to Dr. Phillips' evidence, sir, which commences at Volume 58 on this issue.

THE COMMISSIONER: 38 did you say?

MS. CRONK: I am sorry, 230.

THE COMMISSIONER: I have 230, what is the transcript number.

MS. CRONK: The volume is 58, sir, I don't think you need to refer to the exact portions at this stage, sir. Exhibit 230 is a summary of the various autopsies that have been conducted at the Hospital and you will see, sir, that in 608 cases digoxin specimens have actually been taken and tested. In 97 of the 608 cases digoxin levels ranging between 1 nanogram and 4.9 nanograms were measured on post mortem blood specimens. In 85 of the 97 cases the patients prior to their deaths had been on digoxin. So in the 97 where there was a significant reading, that is between 1 and 4.9, 85 of those patients had

been on digoxin and the post mortem levels were considered normal. That leaves us then, sir, with 12 cases where the patients were known not to have been on digoxin and not to have received it at any point during their life.

Dr. Phillips has testified that most of these 12 patients were neonates save for two or three. You will see, sir, that the highest reading recorded on these 12 patients was 2.1 nanograms per millilitre. Most of the patients were not cardiac patients, their clinical symptoms, Dr. Phillips was not in a position to give evidence as to what their clinical symptoms had been prior to death, and in every case he testified there was a satisfactory pathological cause of death, all were ascribed or attributed to natural causes. So that out of the entire group of 608 tests conducted since March 24th, 1981 there were 12 where the patients had not been on digoxin and the highest reading of those 12 was 2.1 nanograms per millilitre.

THE COMMISSIONER: What about the 34 --

MS. CRONK: Those sir I will be dealing with in a separate context.

THE COMMISSIONER: Yes, all right.

MS. CRONK: I think in my submission the important point at the moment is out of the entire

group there were only 12 here the children were not on digoxin and the highest reading was 2.1 nanograms.

The final piece of research, if you will, sir, or data that has been made available to you through evidence is that attested to by Mr. Cimbura. You will recall, sir, I said a few moments ago that Mr. Cimbura has testified that he tried to simulate in his laboratory at the Centre of Forensic Sciences the research results reported by Dr. Seccombe and his group. He testified in this regard that the purpose in doing so from his point of view was to determine whether or not his HPLC method in fact separated out substance X. He obtained post mortem blood specimens from 24 children and in 20 cases he also had fresh heart tissue available; in four he had fixed heart tissue available; and in two cases he had Klotz solution that had been used in fixing and preserving the heart tissue; none of the 24 children had been known to be on digoxin; 12 of the 24 children were two months old or less, five were premature. The results of the assays Mr. Cimbura has testified did not disclose any digoxin like substance of any kind above the minimum level of detection used on his assay technique which is 1 nanogram. In none of the 24 cases was a level greater than 1 achieved. In short

in his opinion they did not confirm Dr. Seccombe's research.

Mr. Cimbura concluded from this study that one of four things had happened. First, the children did not have substance X. Alternatively, if it was present it was in concentrations of less than 1 nanogram per millilitre. Alternatively, if it was present it did not cross react with the antibodies that he was then using and which he indeed used on all of the tests conducted at the Centre.

Finally, and again as an alternative, if it was present it was in fact extracted or removed by his HPLC extraction process. That evidence, sir, is found at Volume 52, page 1590, the results of his test in this regard are set out in Exhibit 213, sub 8. You will recall, sir, perhaps that Exhibit 213 is a bundle of documents that sets out page by page the various results on each of the studies conducted at the Centre of Forensic Sciences in an effort to refine and confirm on a reasonable scientific basis the reliability of the testing techniques they were using, it is page 8 that refers to this particular study.

On the basis then, sir, of those six different research studies, or if you will six

different sets of testing about which you have heard evidence, I make the following submissions to you concerning substance X and the reliability of the HPLC method to isolate digoxin from substance X.

First, no concentrations of substance X or a digoxin like substance had been reported in any of the literature filed as exhibits before you, or on any of the tests about which you have heard whether conducted at the Hospital for Sick Children or elsewhere on any patient known not to have received digoxin in the range of values that have been measured for these 36 children. The highest value has been that reported by Dr. Seccombe, that is 4.1 nanograms and that was in a premature four day old infant child. I mentioned earlier, sir, that there had been a great number of articles filed before you with respect to this issue and it may be of assistance for you to know what they are.

THE COMMISSIONER: Yes.

MS. CRONK: Exhibit 8 through 12 inclusive, Exhibit 27, 30 and 230, 231, 418 and 213, page 8 as I indicated a moment ago. In short, sir, neither in the reported articles in the literature which we in my submission must take as a reasonable reflection of the state of the art of the scientific

community to date, nor in the direct evidence of any of the witnesses who have appeared before you, has a level in excess of 4.1 nanograms being recorded in a patient known not to have been on digoxin. We simply have not heard about any levels in the range or proportion of concentrations measured here.

10 In my submission, secondly, sir, there is accordingly no data at all as to suggest that substance X can account for post mortem blood levels in the ranges with which we are dealing, or indeed in the case, for example, of Justin Cook and Kevin Pacsai, where we have significantly high ante mortem levels in the range of ante mortem blood levels with which we are dealing.

Third, I note, sir, that none of the studies again either reported in the literature, including Dr. Seccombe's or about which you have heard, in any type of sample, any kind, ante mortem, post mortem or tissue have utilized the testing technique adopted by Mr. Cimbura, that is the RIA Beckman double antibody assay coupled with the HPLC extraction technique followed again by the RIA, none of the studies have been conducted using that methodology where actual ranges of concentrations have been placed before you.

In my submission in the absence of evidence of that kind it cannot be said with any degree of reasonable certainty that the substance where present is not in fact extracted by HPLC, or did not in fact fail to cross react with overall procedures used by Mr. Cimbura.

Fourth, sir, there have been no systematic studies of infants done in the age range of these 36 children having their clinical characteristics, that is congestive heart failure or anatomically deformed hearts, this has been the evidence of both Dr. Seccombe and Soldin.

Fifth, sir, there has been no data to suggest, as Dr. Seccombe put it, that substance X reacts --

THE COMMISSIONER: I wonder if you can just go back to number four, you said no studies of infants, what did you say --

MS. CRONK: In the age range of these 36 children with the varying age of these children having their clinical characteristics, that is congestive heart failure or anatomically deformed hearts.

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THE COMMISSIONER: They couldn't very well do that, could they, unless they had done it on our data. Those are specific -

MS. CRONK: In theory, sir, you will recall in the data that has been made available through Dr. Phillips, and I intend absolutely no criticism - I simply observe that a group of patients who were known to have had congestive heart failure and were known to be within the age frame of our children could have been isolated from a patient death population and such a study undertaken. It needn't have been done at the Hospital for Sick Children: it would have been done anywhere. I simply make the observation for you, sir, that such a study to the knowledge of Drs. Seccombe and Soldin has not been done.

Fifth, sir, there is no data to suggest, as Dr. Seccombe put it, that Substance X reacts biologically in a fashion similar to digoxin. Accordingly in my submission it cannot reasonably be asserted on the basis of current scientific knowledge that Substance X can account for clinical manifestations of digoxin toxicity.

THE COMMISSIONER: I don't know what to draw from that because the only merit of

Substance X if it has any merit is that it will reflect upon our readings.

MS. CRONK: That is correct, sir. The purpose of the submission in that regard is simply to indicate that the characteristics of this particular patient group, our 36 children, include in some instances symptoms prior to death during the agonal events which experts have said are suggestive of digoxin toxicity. And I am saying in assessing the role of Substance X and in interpreting these levels it is relevant for you in my submission to note that there is simply no data before you as to whether or not Substance X can account for those kinds of clinical manifestations at all.

I don't advance this submission in connection with the reliability of the testing technique, but rather as a feature of Substance X that should be borne in mind in assessing these levels.

And finally, sir, there is no data to support that Substance X reacts pharmacologically in a manner similar to digoxin. By that, sir, I mean that there is no hard data before you to suggest that Substance X is subject, for example, to a post mortem multiplier effect or that it would distribute

in tissues in a manner similar to digoxin.

More particularly, with respect to the testing technique used by Mr. Cimbura there is no hard data to suggest that Substance X exits the column of the HPLC at the same time as digoxin or that it reacts to the antibody used in his RIA technique in the same way as digoxin.

Therefore in my submission, sir, whether or not we accept that Substance X is excluded by virtue of HPLA from the kind of digoxin assays conducted by Mr. Cimbura, there is in my submission no supportable basis on which it can be said to account for the very high levels found in these children, and more particularly for the levels found in the tissue specimens of the various children with which we are concerned.

I should note on that issue as well, sir, that Mr. Cimbura because of this issue was asked specifically whether he could have any assurance that what he was taking off the HPLC column as digoxin may not in fact contain some of that unidentified substance which Dr. Seccombe had called Substance X. I think his response in this regard is sufficiently important and I propose to quote from it directly. It is recorded in Volume 2 of Mr. Cimbura's evidence,

at pages 145 to 146. It was as follows:

" Well, I believe I have what I call reasonable assurance to a reasonable scientific degree based on my knowledge of these techniques and the fact that we were able to separate the substances that we have tried and are known to cross-react from digoxin. I have - I am reasonably satisfied that what I am measuring on the HPLC is digoxin.

This belief is strengthened by some more analyses which I had an occasion to perform in the babies under this investigation, some babies under this investigation, where I have used additional modifications of the HPLC in one instance, and in another instance I used the application of the techique mass spectrometry, gas chromotography in one instance, and they all confirmed my results, and the identification of drugs in

forensic toxicology is a matter of probability, and you may increase the probability by various manipulations.

So I suppose to summarize my answer would be I am reasonably satisfied that what I measuring after all our experimental work is digoxin. "

Mr. Lamek then asked him:

" Is it not fair, though, Mr. Cimbura, to say that your experimental work has been directed to the separation of known digoxin-like substances? Isn't that what HPLC is all about?

A. That is right. The potential of the HPLC column, however, is not limited to the substances which are known and which were tested. It has a wide potential for separation. "

Mr. Cimbura then continued and listed six reasons that formed the basis for his opinion that he had in fact extracted successfully digoxin as distinct from Substance X on the HPLC column.

I think I can quickly move through these, sir, before we break for lunch with your indulgence?

THE COMMISSIONER: Yes.

MS. CRONK: The first reason was this - we have already heard about this one, sir - it is the study that his group conducted at the Centre for Forensic Science in an effort to duplicate Dr. Seccombe's results and his group was unable to duplicate those results although they tested specimens from 24 infants known not to have been on digoxin.

Secondly as part of the HPLA test run at the Centre for Forensic Science, Mr. Cimbura had a study conducted to determine the time at which digoxin and some 14 other recognized compounds in fact exited off the HPLA column. The results of this study, sir, are set out in Exhibit 215 that has been filed before you.

The results established that digoxin exited the HPLA column approximately nine minutes after entry of the sample into the column. He testified that the results of the test conducted at the Centre suggest that unknown digoxin-like substances such as Substance X do not exit the HPLC column in the

same time frame as digoxin.

Perhaps more importantly, sir, his third reason was that quite apart from his own studies and his interpretation of the results of those studies he was not familiar with any studies where Substance X had been proven to exit the HPLC column at the same time as digoxin, nor was Dr. Seccombe aware of any such study.

Dr. Soldin testified at volume 9, page 1467 that he thought it unlikely that Substance X would exit at that same time as digoxin.

His fourth reason is a reason to which I have already referred, sir, and that is that the levels of Substance X found and reported in the literature and by Dr. Seccombe's group were in his opinion relatively small, and accordingly he doubted that Substance X could account for the concentrations found in the specimens he tested using HPLC.

Fifth, he was not aware of any study which indicated that Substance X had been detected or measured following use of an extraction process such as the HPLC. As you know, sir, all of the studies that were done including Dr. Seccombe's with the exception of Dr. Soldin's water-loading experiment did not make use of HPLC. It is therefore

a very open issue in the scientific community as to whether or not HPLC - there is no data to suggest that it isn't in fact extracted.

Then finally, sir, he relied upon the case of Jesse Belanger as an illustration for the basis of his opinion in this regard. He indicated that his group analyzed the available specimens on Jesse Belanger on three different HPLC columns and on gas chromotography and mass spectrometry and used two different antibodies.

In each case a positive reading for digoxin was obtained, leaving Mr. Cimbura to conclude it was most unlikely that Substance X had been present unless Substance X was in fact digoxin.

As you will recall, sir, Mr. Cimbura was cross-examined in a manner that can only be described as vigorously by various Counsel as to the basis for this opinion, and the opinion of various other experts was sought as to whether or not it was a reasonable scientific proposition that Substance X in fact did not affect the readings that were obtained in these 36 cases.

I propose briefly to review what the evidence of others has been on that and perhaps I would do that after the break.

THE COMMISSIONER: Yes. We will rise now until 2:15.

---Luncheon Adjournment

AA-1
RD/hr

---On resuming

THE COMMISSIONER: Yes, Ms. Cronk.

MS. CRONK: Thank you, sir.

Before the break, sir, I was outlining for you my submissions with respect to the reliability of the testing procedure that had been used by Mr. Cimbura and conducting his various digoxin assays and I was about to refer you, sir, to certain of the evidence by other pharmacologists, with respect to that test methodology. Dr. Spielberg testified that on the basis of the currently available scientific information, if a substance was identified as digoxin after the testing of, in the case of tissues, a sample using both HPLC and RIA as, of course, was done by Mr. Cimbura in some cases, the probability is that the child was administered digoxin during life.

THE COMMISSIONER: Whose evidence are we --

MS. CRONK: Dr. Spielberg.

THE COMMISSIONER: Yes.

MS. CRONK: It is found, sir, at Volume 54, pages 2127 to 2129 .

He testified further that if digoxin was found in a specimen by analysis using mass

A-2

spectroscopy the liklihood is that the patient received digoxin and that digoxin was, in fact, present as measured.

Dr. Kauffman, sir, testified that on the basis of his discussions with Mr. Cimbura, and on the basis of his personal review of the centre's laboratory data, his understanding was that the HPLC technique that had been used had extracted the breakdown products of digoxin and endogenous substances. He indicated that it was possible to separate digoxin itself, on the HPLC from other substances, both known and unknown substances, that did not co-migrate with it on the HPLC column and you will recall the evidence is, sir, that there is no hard data to suggest that there is a similar co-migration by its substance X with digoxin on the column.

The soundness of Mr. Cimbura's opinion, as to what, in fact, he was measuring was, and I think I can say this fairly, challenged by only one witness before this Commission and that was Dr. Soldin. Dr. Soldin testified that in his opinion, to ensure that digoxin was being separated from substance X by use of the HPLC method, a detection system, other than RIA, should be used. He recommended mass spectrometry and opined that if HPLC was used in combination with it you could

AA-3

then, with certainty, say that the compound thought to be digoxin was or was not pure digoxin. You will recall, sir, of course, this is precisely what was done in the case of at least two children by Mr. Cimbura, Jessie Belanger's tissue specimens and Stephanie Lombardo's tissue specimens.

Dr. Soldin, in the course of giving that evidence, requested as well, that any remaining tissue specimens from these children be made available to his laboratory or others for further testing, using the techniques that he preferred, the HPLC and mass spectrometry.

Subsequent to the evidence of Dr. Soldin in that regard, you will recall, sir, that the Hospital for Sick Children convened a meeting of experts on Monday, March 19th, 1984, to meet the stated purposes of a meeting included, and I am referrring now, sir, directly to Exhibit 399 which is the minutes from that meeting that have been filed before you. The purposes were, first, to determine a set of criteria for the identification of digoxin, using either gas chromotography or mass spectrometry RIA in combination with HPLC or other appropriate analytical techniques.

The third stated purpose of the meeting was to offer an opinion as to the validity of any further analyses, including gas chromotography and mass spectrometry and/or RIA with HPLC as a means of offering a definitive confirmation or denial of the presence of digoxin in the tissues of four children, Jessie Belanger, Justin Cook, Jordan Hines and Stephanie Lombardo. Those are the four, of course, sir, who were never known to have received dixogin in a prescribed sense during life.

The minutes of the meeting and the report prepared by the Chairman of the Meeting, Dr. Gilbert Hill of the Hospital for Sick Children, have been filed before you, sir. The report is Exhibit 400 and I refer briefly to certain portions of the report on page 2 and paragraph 5.2 contains the following statement:

> "In the context of the cases under discussion,(that is Cook, Lombardo, Belanger and Hines,) the panel placed a much higher degree of reliance on the high pressure liquid chromotography combined with radioimmunoassay data than on the GCMS data. This preference was based on the known problems and

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> interpretation of the GCMS data and on a high degree of confidence in the HPLC/RIA technology. This confidence was strengthened on learning of the way in which the HPLC/RIA had been applied".

Them it goes on to record the example of Justin Cook and Jessie Belanger in the matter in which samples from those children were tested.

On the same page, sir, at paragraph 6.1 it reads:

> "In the context of the cases under discussion it was agreed that a positive test for digoxin obtained by an acceptable analytical procedure would be considered as presumptive evidence for the presence of digoxin in the material being examined. An acceptable analytical procedure was defined as one in which a specimen was subjected to HPLC followed by RIA."

Then at paragraph 6.3, sir:

> "It was recognized that the development of a definitive GCMS method for digoxin in tissues was a highly desirable goal and would be an extremely valuable

AA-6

> contribution to forensic science. However, it was felt that the current state of the art was such that no assurance could be made that the further use of GMCS would provide in the near future an unequivocal answer to the question of whether or not digoxin is present in the tissues available for examination."

The conclusions in my submission, sir, reached by the participants in the conference were essentially twofold, as they concern this Commission.

First, the group felt that there was no useful purpose in conducting any further tests on the materials available, that is the remaining specimens in order to detect digoxin. Secondly, sir, the group was, in my submission, beyond question, satisfied that the procedures followed by Mr. Cimbura in the Centre of Forensic Sciences, were satisfactory in detecting digoxin with respect to the test that he did do by way of RIA, HPLC and RIA.

In light, sir, of Mr. Cimbura's evidence, regarding the methodology employed to conduct the various tests, and in light of the conclusions reached by this panel of experts as recorded in Dr. Hill's

AA-7

report and in the minutes there is, in my submission, sir, no reasonable basis on the evidence before you to suggest or infer that the test results obtained at the Centre of Forensic Sciences using RIA plus HPLC and RIA are unreliable by virtue of the type of technique utilized, or by virtue of the potential for non-exclusion of substance X.

If I may, sir, I then purpose to now turn to the interpretation of the digoxin concentrations found in ante mortem and post mortem specimens. It is apparent from the universal evidence before you from various experts that there are a number of difficulties associated in an interpretation of these results. The difficulties arise in three general categories: first, with respect to sampling technique; second, some are specific to the type of sample involved, as for example in the case of tissues, whether the specimen be fresh, fixed or exhumed; and third, some relate to purely pharmacological issues, such as the distribution pattern of digoxin following administration, or, for example, relationship between high serum potassium levels and high digoxin levels.

I propose, sir, to deal with the problems outlined by the various experts. Mr. Lamek,

AA-8

RD/hr

in due course, will be making submissions to you as to the significance to be attached to the actual levels. Where an issue has arisen on the evidence concerning the integrity of the sample, itself, the sampling technique or the storage conditions of the sample, I will be dealing with those issues in my submissions. The index that I provided earlier, sir, highlights the eight main issues that highlight the difficulties and interpretation of these levels. The first has to do with the time at which the sample is taken. It is clear, in my submission, from the evidence of all the pharmacologists that when digoxin levels are measured in ante mortem serum, essentially what is being measured is digoxin that is then having neither a therapeutic or a toxic effect. That is so, sir, because the evidence has been that digoxin has no biological activity or pharmacological effect at all until it reaches tissues in the body.

There is no dispute on the evidence that blood specimens must, therefore, be obtained long enough after the last dose of digoxin has been given to ensure that what is, in fact, being measured is the concentration of digoxin at steady state or not early in the distributive phase or the Alpha Phase.

AA-9

You recognize, sir, if, in fact, the sample is taken too early, very high concentrations will inevitably be measured, leading to a potential for a very great misinterpretation of the results.

In light of these difficulties, Dr. Spielberg has testified that at the Hospital for Sick Children, it is recommended that a blood specimen be taken for digoxin assay at least six hours after the last known dose of digoxin was administered and that it is, in fact, preferable to wait twelve hours after the last dose, that is until just before the next dose is to be given.

....

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Drs. Kauffman and Mirkin agreed that that was the general clinical guideline, the preferred standard for timing. It was of course obviously even more important if the dose had been given orally. Because you will recall, sir, that if taken within the first two to three hours after the oral dose is administered the peak concentrations of digoxin in blood will in fact be measured rather than the fully distributed concentration at steady state. There is, however, in my submission, sir, no evidence whatsoever to suggest that any of the blood levels obtained on any of these 36 children, save one, were obtained too close in point of time to the time of the last known administration of dixogin. For obvious reasons, sir, I place emphasis on the last known administration of digoxin. In the circumstances where an unauthorized dose is postulated, as it will be with respect to some of these children in Mr. Lamek's submission, two pieces of vital information are missing, that is the time at which it was given and the route by which it was given. Where in the cases before you we have concrete data as to the time of the last known dose, it would appear that one ante mortem sample was taken too close in point of time to the time at which the last dose was given,

and that is in the case of Richard McKeil and I will have more to say about that in due course, sir.

Although as I have indicated the two pieces of information that are necessary to determine definitively whether or not the samples had been taken in a timely fashion are not available, that is the route of administration and the exact time of administration, we are however assisted in some cases by virtue of the fact that concentrations of the drug were in fact measured in tissue specimens, which of necessity on the evidence of the pharmacologists means that some distribution in those cases had to have taken place from blood in the tissues.

The site of the sample and the sampling techniques give rise to difficulties of interpretation as well, sir, both in the context of ante mortem blood specimens and post mortem blood specimens. Dealing first with ante mortem specimens; we have heard from Dr. Spielberg for example that you must know the site of the ante mortem blood specimen in order to ensure that it was not drawn, for example, from a catheter line which is often used at the Hospital for Sick Children both to administer medication and to draw blood. If the sample was drawn from a catheter line he indicated that extremely

high digoxin levels can occur, although not truly reflective of the concentration of digoxin in the serum of the patient.

Mr. Cimbura, although by his own admission inexperienced in the testing of ante mortem blood specimens, inasmuch as he is a toxicologist and forensic scientist, suggested that the particular site of the ante mortem blood specimen would not in his opinion make a material difference so long as there was no issue over the timing of the sample. He stated that so long as the sample was taken from an intact vein or artery he would not be concerned about its source.

The real problem with respect to sample site and sample techniques, sir, arises in the context of post mortem blood samples. The experts are unanimous that the site from which the blood sample is taken post mortem and the manner of its being taken is of importance to the interpretation of the level. An issue has been raised in this context specifically with respect to the post mortem blood specimens from two children, Janice Estrella and Kristin Inwood. Dealing first with the case of Kristin Inwood; Dr. Spielberg has raised the issue having regard to the very high concentration that

was measured in the post mortem blood specimen of Kristin Inwood, you will recall, sir, that it was 491 nanograms per milliliter. He suggested that it was relevant to know where the specimen came from to ensure that no piece of tissue was inadvertently included with the specimen. Once that evidence had been given, sir, with the assistance of Mr. Roland, the Counsel for the Hospital, it was determined through the Hospital that the specimen was a sample of blood taken at autopsy and subsequently sent to the Virology Lab where it was refined in accordance with the procedures there, such that the sample actually sent to the Centre of Forensic Sciences was a serum sample. Drs. Taylor and Cutz who conducted the autopsy on Kristin Inwood testified that in the normal course the site of such samples at autopsy was the inferior vena cava a vein. When informed of this information, that is was in fact serum and that Drs. Cutz and Taylor in the normal course took such samples from a vein, Dr. Spielberg agreed that the possibility of the inclusion of a piece of tissue in this specimen and hence the possibility of contamination from that source had been ruled out.

Generally Mr. Cimbura has testified

that there are three main sites for the drawing of post mortem blood. They are from the heart, the peripheral vein and the sagittal sinus in the brain. It was his evidence with which Dr. Spielberg agreed that concentrations of digoxin found in post mortem blood specimens from the heart are generally higher than concentrations measured in sagittal sinus blood samples taken from the brain.

Dealing then with the case of Janice Estrella and the issue of potential contamination which arises by virtue of the site of the post mortem blood samples and the manner in which they were taken. I don't propose to review at length the evidence as to how they were taken at this stage, sir. You will recall that Dr. Taylor who was the pathology resident at the Hospital for Sick Children who conducted the autopsy, has testified that he obtained two post mortem blood specimens, one from the severed iliac or leg vein into which he inserted the end of the syringe while someone else massaged the leg, and the other from the pelvic cavity. The pelvic cavity sample yielded a level of 72 nanograms per millilitre when tested. The leg vein sample a reading of greater than 4.7 nanograms, and there was insufficient sample for further testing. When it was

discovered that the second sample had been obtained from the pelvic cavity the possibility of an artifact-ually elevated concentration of digoxin was directly raised.

We have heard from Dr. Phillips of the Hospital for Sick Children and from Mr. Cimbura that in the late summer and early fall of 1982 a study was undertaken at the Hospital for Sick Children in conjunction with the Centre of Forensic Sciences for the purposes of determining whether there is a discrepancy between pelvic cavity digoxin concentrations and digoxin concentrations in veins and arterial blood specimens. This you will recall, sir, of course was the gutter blood study so called and the results are set out in Exhibit 213 and 238. The protocol established and used for the study has also been filed as Exhibits 202B and 202C.

To summarize what was done in the study, sir, it was intended according to both Dr. Phillips and Mr. Cimbura that the Estrella situation be simulated insofar as was scientifically possible, 14 cases were involved in the study, 2 specimens were taken in each case from the pelvic cavity, one at the start of the autopsy and a second some three hours later. Dr. Phillips evidence in this regard,

sir, is found at volume 58, commencing at page 2975. Mr. Cimbura and Dr. Phillips have both testified that with the exception of one case, case no. 5, all of the results measured on the pelvic cavity samples both at the commencement of the autopsy and three hours later did not exceed the range of values found in post mortem blood specimens from infants on digoxin therapy. In the one case of course, sir, you will recall that the levels measured were 169.6 nanograms from the sample taken at the beginning of the autopsy, and 17.7 nanograms from the sample taken three hours later. According to Mr. Cimbura the high result, that is the first specimen was abnormal and artificially elevated likely as a result of contamination. Dr. Phillips agreed.

The significance of the results in the context of the various opinions expressed, sir, will be dealt with at some length by Mr. Lamek, but for present purposes I have two submissions with respect to the implications of the results of this study in the context of Janice Estrella.

The first is very obviously the results underscore the importance of knowing precisely with post mortem blood specimens the site from which the sample was taken and the manner in which the sample

was taken. In this case some experts have testified here that in light of case no. 5 on the gutter blood study, the Estrella level although it cannot be discounted entirely cannot be relied upon with the same degree of confidence as can other levels.

Secondly, it is also clear on the basis of the gutter blood study in my submission, that blood in the pelvic cavity may, and only may, for it happened in only one of the 14 cases, yield digoxin levels grossly out of line or inconsistent with levels measured in heart and sagittal sinus blood specimens.

If I can turn then, sir, to the issues that have been raised concerning storage conditions for blood specimens. This issue arises primarily again in the context of the post mortem blood specimen taken from Kristin Inwood. Dr. Spielberg expressed the opinion, again in the context of discussing the possibility that it was artifactually high and hence a false positive reading of digoxin in that sample, that the freezing of a blood sample in a refrigerator, if the refrigerator is self-defrosting in effect means that a small specimen of blood is freezing and defrosting and refreezing.

CC
EMT/cr

He suggested that if this in fact occurs two possible areas of difficulty arise. The first is that it can result in some degree of evaporation of the sample itself leading to loss of volume which in turn can result in the elevation of drug concentrations present in the sample. The second difficulty or at least a possible second difficulty is the possibility of cross-contamination between the specimen of interest, the blood sample, and other things present in the refrigerator.

In fairness to Dr. Speilberg, sir, I hasten to point out that he did not suggest that either of these possibilities had in fact taken place with the Kristin Inwood sample. He simply raised them as possibilities and areas of concern if in fact it happened that way.

The suggestion that the sample having been frozen as I understood Dr. Speilberg's evidence arises from the fact that this particular serum sample was discovered in the virology lab at the Hospital for Sick Children some nine or ten months after the child's death. It was delivered to the Centre for Forensic Science for testing in January, 1982.

There is, however, sir, in my submission

2 no clear evidence before you at all that the sample was in fact frozen, although we do know that it was heated prior to testing.

The origin of the suggestion that it was frozen appears to flow from a passage included in the minutes of a meeting held on September 13, 1982 between various experts and representatives of the Metropolitan Toronto Police Force.

At page 5 of those minutes, sir, which have been filed as Exhibit 261, Sargeant Warr of the Metropolitan Toronto Police Force is quoted as having advised that the sample had been stored,heated and apparently frozen.

If in fact the sample was frozen, sir, Dr. Speilberg's concerns as to possible contamination must be weighed in my submission in the context of opinions expressed by the other pharmacologists.

Dr. Mirkin has testified that it is a very common practice in his department in his hospital to freeze serum or plasma specimens for subsequent digoxin assay. Dr. Kauffman agreed, and indicated that that too was a common practice in his department. Dr. Mirkin expressed the opinion that in such circumstances if in fact the specimens have been frozen, that the concentrations remain fairly stable

3 and that he would not expect too much evaporation even if it had been refrigerated for a very long time and the stopper had been left off. If in fact evaporation did occur in a material fashion, which he thought was a low likelihood, the relative concentration of digoxin in the specimen would, as Dr. Speilberg suggested, have increased.

Dr. Kauffman --

THE COMMISSIONER: I don't know that it would increase much. This is the highest - certainly the highest level we ever heard of.

MS. CRONK: That is correct. The suggestion is it would increase over what the true reading had been at the time the sample was taken.

THE COMMISSIONER: Oh, I see. Yes.

MS. CRONK: Dr. Kauffman agreed that the possibility of evaporation due to lengthy freezing or refrigeration could have a similar effect, and it was for that very reason, sir, as you will hear from Mr. Lamek that in attempting to interpret this level he took what he described as a very conservative approach and assumed that the actual concentration in the blood specimen at the time of death could well have been one-tenth the measured concentration.

He assumed, therefore, that the level

could have been as low as 49 at the time it was taken, which he considered to be a worst case scenario for the purposes of interpretation.

Even using that approach, that is the worst case scenario, Dr. Kauffman considered that level of 49 to be a high one, signifying a contribution by digoxin to the child's death.

His evidence, sir, in that regard is found at Volume 72, page 5838, Volume 74, page 6469.

We do know as I have suggested, sir, that the sample had been heated before it was assayed. Mr. Cimbura in light of that information once provided to him ran an experiment on heated serum simulating the temperature in heating which he understood to have occurred in the Inwood sample.

He has testified the results of that study indicated no significant change in concentration following heating as compared to the concentration measured prior to the sample being heated.

As you may recall, sir, quite apart from the study that was done by Mr. Cimbura, Dr. Graham Ellis testified that on March 24, 1981, he re-assayed a serum sample taken at autopsy from Justin Cook. In doing so he heated the sample for 30 minutes at 56 degrees.

When originally assayed two days earlier, on the Sunday, March 22nd, a level of greater than 100 nanograms per millilitre had resulted. When re-assayed following heating by Dr. Ellis two days later, the heating of the sample made no material difference to the concentrations of digoxin measured. The assay result, Dr. Ellis testified, was in the order of 100 or slightly greater. That evidence, sir, is found at Volume 49, page 1021.

Dr. Stewart MacLeod had something to say about this issue of heating as well. He agreed in the result with Mr. Cimbura as did Drs. Mirkin, Kauffman and Hastreiter that heating would not be expected to result in an artifactual change in the concentration of digoxin present.

Dr. Mirkin, however, drew a distinction with actual boiling of the sample as opposed to pure heating, and suggested in those circumstances evaporation obviously could occur resulting in a change in concentration.

It is quite clear, Mr. Commissioner, in my submission thatthe true and complete history --

THE COMMISSIONER: I am sorry, what evaporates? What is it that evaporates?

MS. CRONK: Part of the volume of the

sample which therefore influences the concentration in the remaining sample.

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THE COMMISSIONER: But does it depend on what evaporates, if the digoxin evaporates or if the blood evaporates?

MS. CRONK: Well, as I understand it, sir, if part of the volume of the sample diminishes then the concentration, including in part part of the drug if that occurs, or if it does not include part of the molecules of digoxin, in fact that --

THE COMMISSIONER: All I am asking you really is did they indicate which was likely to evaporate? Was it digoxin or was it --

MS. CRONK: I am not sure, sir, that they were asked that specific question. The results, their opinions as to the likely results were sought and expressed but I am not sure that they distinguished between them.

THE COMMISSIONER: Did they say it would be a greater concentration --

MS. CRONK: The implication, sir, is that it would be artificially elevated.

THE COMMISSIONER: I suppose that is so. I don't understand why.

MS. CRONK: Well, the problem --

7

THE COMMISSIONER: Only if everything else evaporates except digoxin.

MS. CRONK: The proposition as I understood Dr. Speilberg's evidence was that subjecting the sample to heating could reduce the overall volume of the specimen and in that context alter the balance of the concentration in the remaining specimen such that it would be increased.

THE COMMISSIONER: It could. It could, I know that.

MR. SCOTT: If you take rye and water --

MS. CRONK: My friend is suggesting another explanation. I am going to leave that to Mr. Scott to develop.

MR. SCOTT: I said if you make a rye and water, half rye and half water and you put it on your deck for two days and let half the volume evaporate you will not have a stronger drink.

THE COMMISSIONER: A weaker drink?

MR. SCOTT: No, unless it rains you will have a drink of exactly the same strength. Now I have done work on that.

THE COMMISSIONER: If it evaporates, if we evaporate a solution containing digoxin why

doesn't the digoxin go with it, with the evaporation?

MR. SCOTT: Miss Cronk didn't ask the witness when we brought the witness.

THE COMMISSIONER: I am not going to call them all back to ask that question.

MS. CRONK: If I had only known, Mr. Scott, the explanation at the time the evidence was given by Dr. Speilberg, the matter could have rested there, sir, but in any event as I understand it --

MR. SCOTT: I wanted to while we are at it congratulate Mr. Lamek for his chivalry in a assigning this fascinating topic to his junior associate. She is handling it very well but I think it is an example of forebearance on his part to give up a topic like --

MS. CRONK: I am always grateful for gratuitous comments from senior counsel, and delighted when they emanate from Mr. Scott.

To return to the issue of heating then, sir, in one very short submission it appears that it doesn't make a difference in the opinion of the majority of the experts.

THE COMMISSIONER: It does or --

MS. CRONK: Does not make a difference to the integrity of the sample and hence the concentrations

9 that are measurable.

The very clear feature of the evidence in this particular area, Mr. Commissioner, is that the full and complete history of the sample is very much a mystery. We don't know all the details of what happened to it, where it was stored and what procedures were followed before it was delivered to the Centre for Forensic Sciences.

In all the evidence before you, however, in my submission the likelihood of artifactual contamination by virtue of freezing, refrigerating, heating, defrosting, unless it rained as Mr. Scott suggested, is minimal.

THE COMMISSIONER: How can it in a refrigerator?

MS. CRONK: One never knows, sir. And for that reason in my submission the significance of the digoxin concentration in this sample cannot be rationally and reasonably challenged on that basis.

The analytical technique used to carry out the actual assays very obviously, sir, had an implication for the interpretation of the level. We reviewed that in some detail. The efficacy of the HPLC and the RIA technique and as well the opinions

of the various experts as to whether or not Substance X has any role to play in interpreting these levels.

We come then to what has been described by the pharmacologists as the redistribution characteristics of digoxin both during life and after death. I propose to deal with the characteristics of it during life first.

The issue which arises here, sir, as I apprehend the evidence, is that under certain circumstances digoxin can redistribute or unbind from tissues while the patient is still alive resulting in a release into blood of the drug leading again to artifactually high concentrations of digoxin in the blood samples when they are in fact measured.

There appears on the evidence to be no disagreement that the phenomenon in fact occurs. The reasons for its occurrence and the mechanics by which it occurs are not fully understood.

Although now all the pharmacologists were agreed as to the cause as to why it happens, there were certain features upon which they did agree, and I refer now principally to the evidence of Drs. Kauffman, Mirkin and Speilberg.

First, as a result of the pharmacological activity of other drugs on the body, this phenomena

has been known to happen. They referred, for example, to the drug quinidine which is associated with abnormally high levels of digoxin in patients receiving both drugs. It has been suggested as well that as a result of certain pathophysiologic conditions, a reported one, the most well known one, renal failure, the same phenomenon can occur.

The third suggested circumstance in which it might apply, might take place, is as a result of tissue death during life or damage caused by the inherent disease state of the patient.

Specifically in this context Dr. Speilberg has advanced the theory that resuscitation trauma may in fact cause redistribution of digoxin during life from tissue into blood, thus resulting in falsely elevated blood levels.

The area of dispute among the pharmacologists is not thus whether or not it happens, but when it happens and whether or not it has any application to the levels that are of interest to you.

Dealing first with the case of Gary Murphy, sir, you recall that he was a patient who died at the Hospital for Sick Children on April 23rd, 1983. His last ante mortem digoxin level was obtained

some 19 days prior to the date of his death and produced on a serum sample a level well within the therapeutic range. It was 1.5 nanograms per millilitre.

Dr. Speilberg has pointed to the case of Gary Murphy in support of two propositions: one that we are concerned with now, and that is the possibility of redistribution of digoxin during life, and secondly (and we will come to this in a moment) the possibility of redistribution of digoxin after death.

In Gary Murphy's case a post mortem blood specimen was also taken by intracardiac puncture some four and a half hours after his death. It yielded a reading of 18.7 nanograms at the Hospital for Sick Children. A sagittal sinus blood sample was taken at autopsy some 10 hours after death, resulting in a reading of 18.7 nanograms again at the Hospital for Sick Children. So that we have then on the Hospital's readings for Gary Murphy an ante mortem and two post mortem blood readings.

In addition post mortem blood readings were tested at the Centre for Forensic Science as were various tissue specimens. At the Centre a specimen of blood taken at autopsy yielded a level of 32.2 nanograms per millilitre. A specimen of

13 sagittal sinus blood as distinct from heart blood yielded a level of 18.9 nanograms per millilitre.

Dr. Kauffman in testifying at the Murphy Inquest was asked to outline what he felt were the possible explanations for what was obviously a very high post mortem blood serum level in the case of Gary Murphy. He outlined five hypotheses which he felt might explain the levels.

His preferred hypothesis, however, he expressed in this language. It is found, sir, at Volume 72 of our transcripts, page 5817 to 5821.

"The fifth hypothesis or theory ..." This is as described by Dr. Kauffman.

> "...is that the gradual worsening of his cardiac condition, the continuing and progressive damage to his heart muscle, his increased lack of oxygen, which is called cyanosis, his reduced output of his heart, cardiac output, the profusion of his tissues resulted in damage to these tissues either functionally or in some cases by the autopsy actual cell death of some tissues, thereby releasing bound digoxin into the serum compartment or

"into the extra cellular fluid which would then diffuse back into the serum.

14 There is very little known, if anything, in the literature about the effects of these kinds of severe physiological derangements of the binding of digoxin and so it is difficult to present objective or conclusive evidence to support this hypothesis, but from what is known about the characteristics of the binding sites I discussed this morning and the nature of the binding of digoxin to this material, this is certainly pharmacologically reasonable and rational."

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RD/ko

Dr. Kauffman thus in Gary Murphy's case, sir, advanced the hypothesis of redistribution during life as an explanation for this child's levels. He thus agreed with Dr. Spielberg specifically that the phenomena can occur and, as well, where it does occur it can account for , what I think fairly can be described, as grossly elevated post mortem blood levels.

Mr. Lamek will be dealing, in his submissions, with the opinions of the various pharmacologists, as to the cause of Kevin Pacsai's digoxin levels, but for the present purposes, sir, the evidence from Dr. Spielberg is that the hypothesis of Dr. Kauffman, in the case of Gary Murphy, might well, in his view, provide an explanation for the post mortem and ante mortem digoxin levels of Kevin Pacsai. In short, Dr. Spielberg suggested that the particular pathophysiology of Kevin Pacsai, as he sees it, might explain the elevated levels found, both ante mortem and post mortem, on the basis of redistribution of digoxin during the life, due to tissue death or necrosis of various specimens, as well as a host of other features.

There is a dispute between Dr. Spielberg, Dr. Kauffman and Mirkin, as to the likelihood of this phenomena accounting for Kevin Pacsai's digoxin levels.

2

Drs. Kauffman and Mirkin disagree that that is the best explanation in the case of Kevin Pacsai.

Dr. MacLeod, in this regard, testified that Gary Murphy was, in his opinion, a very unique case with a very unique kind of physiology and, as well, very unique clinical symptoms. Dr. Kauffman compared the two cases in his evidence, and listed a series of similarities, in his view, but also listed what he thought were overwhelming discrepancies in comparison between the two. He said in this regard, sir, that the basic diseased state of Gary Murphy was fundamentally different than that of Kevin Pacsai. Gary Murphy had a very serious heart lesion, according to Dr. Kauffman, which had resulted during his life in severe cyanosis. In contrast, Kevin Pacsai, as you know, had an anatomically normal heart and was not, according to the clinical record, known to have experienced severe cyanosis at any point during his short life.

The second major difference is that Kevin Pacsai was a much younger child. Gary Murphy was approximately six or seven months of age and, of course, the digoxin concentrations being as age, dependent as the experts suggest they are, Dr. Kauffman felt this was a material distinction as

DD 3

well.

Neither of the two children in Dr. Kauffman's opinion had experienced renal failure, nor were there any clinical symptoms prior to Kevin Pacsai's death, in Dr. Kauffman's opinion of pre-renal failure. That is an opinion held by the majority of the cardiologists who testified before you.

The issue of redistribution effect, if you will, on post mortem and ante mortem digoxin level has been raised, as well as in the case of Allana Miller, sir. Again, Dr. Spielberg expressed the opinion that compared to all the other cases which he reviewed, and you will recall, sir, that he was not asked to, nor did he review all of the 36 children who were before you, but in the cases that he did review there was evidence at autopsy with Allana Miller of a large amount of damage, as a result of the resuscitation process. He has testified that when extensive efforts to resuscitate a child are undertaken, as undisputably occurred in the case of Allana Miller, including the insertion of a pacemaker, electric defibrillation in the administration of multiple cardiac medications, damage can be caused to the myocardium. He suggests that if a blood sample was taken from Allana Miller, from the chamber of the heart, in which necrosis was, as shown

DD 4

by the autopsy results to be occurring, or if a needle was inserted through the damaged myocardium, the possibility exists the dying tissue in the heart could contribute significantly to the concentration of digoxin in the blood. In short, digoxin would become unbound from the heart tissues and would be released into the blood and when the blood specimen was then drawn from the same chamber of the heart and tested a very high level of digoxin in the blood would be measured, as distinct from the tissues.

There is, however, Drs. MacLeod and Kauffman, in fairness I should point out, agreed that as a pharmacological concept it is possible that resuscitation trauma could cause redistribution of digoxin during life. There is, however, once again a dispute amongst the pharmacologists, as to whether or not that phenomenon can be said to account for Allana Miller's digoxin levels.

You will recall, sir, that her post mortem serum level was 69 nanograms per millilitre, as measured at the Centre of Forensic Sciences and 78 nanograms, as measured at the hospital.

Drs. Spielberg and MacLeod have expressed the opinion that resuscitation trauma and redistribution could account for those levels, while

DD 5

Dr. Kauffman thinks it very unlikely.

There is a further aspect to the issue with respect to Allana Miller, as well. Drs. Cutz and Taylor have testified that the post mortem blood specimen drawn from that child was taken by Dr. Taylor from the inferior vena cava, the place from which the autopsy blood specimens were normally taken, using in this case a needle and a syringe. Dr. Cutz observed personally the taking of the sample and testified that on the basis of his observations he was not concerned that the sample had been contaminated in any way, nor was Dr. Taylor. That evidence, sir, is found at Volumes 43, page 8797, and 44, page 8934, respectively.

It is thus clear, in my submission, Mr. Commissioner, that at least one of the concerns raised by Dr. Spielberg, as to the method by which the post mortem specimen was taken does not apply in this case and does not answer the fact that her levels were as high as they were. That is, the sample was not taken from the myocardium, was indeed taken from the inferior vena cava, such if necrosis was occurring in the heart tissue of Allana Miller we don't run the risk in this case of that necrosis affecting the blood serum from the heart that was tested, it having come from a different site.

DD 6

That, of course, does not resolve whether or not resuscitation trauma generally can account for an elevation in this child's levels and on that aspect, sir, of course, there is a dispute amongst the experts.

A difficulty arises, as well, sir, when we come to discuss the possibility of redistribution of digoxin after death, as distinct from necrosis of tissues during life, as distinct from other causes of unbinding during life due to the interaction of other drugs, such as Quinidine, things of that kind. This phenomena in a post mortem sense has been referred to before you, sir, as the post mortem multiplier. The concept again is not a dissimilar one. The suggestion is that when digoxin in tissue -- when digoxin has been taken up by tissue in the body death can result in a displacement of digoxin, otherwise stored in tissues, back into serum, such that post mortem serum samples would then reflect a higher level of digoxin than, in fact, was truly present in the child.

The pharmacologists and Mr. Cimbura are agreed on a number of features with respect to this phenomena. First, an elevation in post mortem blood does not uniformly occur, nor does it occur at any predictable rate of multiplication. There are some

DD 7

patients who simply for unknown reasons don't elevate their post mortem blood levels at all. As I said, there is complete agreement on that score amongst the pharmacologists and Mr. Cimbura.

Secondly, the degree of difference between the ante mortem blood sample and the post mortem blood sample, that is the range of the multiplier is influenced by where the post mortem specimen is taken. Mr. Cimbura, for example, has testified that a blood sample from the heart post mortem will generally have a higher level of digoxin than a blood specimen taken post mortem from the sagittal sinus. So it makes a difference, according to where the sample is taken. Again there is no disagreement on that issue.

Third, the theory or basis for the phenomena is that after death when membranes and cells are dying there is effectively a diffusion of digoxin, a displacement, if you will, from tissues to blood, but of significance from areas of high concentration of the drug to areas of low concentration of the drug. I will return to that, sir, but that concept, in my submission, is important to assessing how high, in fact, the post mortem multiplier is known to be.

There are two main issues then that arise

DD 8

in this context. First of all, what is the range of the multiplier, how high can it fairly and rationally be said to be and, secondly, when will it occur, recognizing that it doesn't always occur. Dealing with the range, first, how high it is. In my submission, sir, on a fair reading of the evidence of the pharmacologists,taken as a whole, a generous interpretation of the literature and their evidence indicates that it can increase, although not always, by anywhere from one to four-fold, assuming no renal failure at the time of death.

My basis for saying that, sir, is the nature of the actual evidence given by the various pharmacologists. Dr. Spielberg has testified that post mortem serum levels can increase sometimes two to three-fold, although the measure of the increase is highly variable. Dr. Kauffman placed it at one to three, recognizing again great variability, but indicated further that he had recently become aware of a paper published by Dr. Hastreiter, which recorded a multiplier effect of up to four. Dr. Kauffman then amended his range, if you will, as anywhere up to four-fold.

Dr. MacLeod, on the basis of research conducted at the Hospital for Sick Children, indicated initially that he thought the range was anywhere from zero

D 9

to five. He did so, sir, in reliance on the recorded results from post mortem blood specimens maintained and recorded by Dr. Phillips. You will recall, sir, that I referred earlier this morning to the fact that since March 24, 1981, some 608 autopsies had been conducted, assays, I am sorry, had been conducted at the Hospital for Sick Children. Dr. MacLeod originally suggested that these results when analyzed indicated a multiplier of anywhere from zero to five. At another point in his evidence he suggested that the mean of the results indicated a post mortem multiplier range of 3.8. When cross-examined by the various Counsel on Dr. Phillips' results, however, it was suggested directly to Dr. MacLeod that the post mortem multiplier was in fact as high as 8, 9 or 10 in some cases, if you actually look at Dr. Phillips' numbers. It is for that reason, sir, in my submission, Dr. Phillips' own evidence in this regard is very relevant to you.

He testified that the total number of autopsies from March 24, 1981 to August 31, 1983 were some 796. Of those, as I suggested earlier, there were 608 cases where post mortem digoxin levels were obtained. You will remember, sir, you asked me earlier this morning, what about these 34 cases that I see on Dr. Phillips' exhibit, where concentrations were greater

DD 10

than 5 nanograms were measured and I said that I would return to that.

THE COMMISSIONER: What number is that?

MS. CRONK: Exhibit 230, sir. The one you were referring to this morning. That sets out the number of autopsies and the number of digoxin assays conducted.

In 34 of the 608 cases then, Dr. Phillips measured results of greater than 5 nanograms. That was for the period, you will recall, sir, from the end of March, 1981 to the end of August, 1983. Subsequently, by the time he came to testify before you there had been three more cases where post mortem digoxin concentrations of greater than 5 had been measured. In consequence, since March 24, 1981 there have been 37 cases at the Hospital for Sick Children where post mortem digoxin concentrations on serum samples have resulted in levels greater than 5.

The particulars of the 37 cases, you may remember, sir, are set out on a computer printout provided by Dr. Phillips. That is Exhibit 232, as amended with certain corrections, set out in Exhibit 232A.

Dr. Phillips explained, in giving evidence, with respect to these results and this

DD 11

printout, that all 37 patients had been on digoxin therapy. All of them were known to have received the drug. Not all of the 37 were infants, nor were they all cardiac patients. In 21 of the 37 cases --

THE COMMISSIONER: I'm sorry, all on digoxin?

MS. CRONK: All on digoxin, sir.

THE COMMISSIONER: Does digoxin have some other use than cardiac?

MS. CRONK: By that I mean not all were in the hospital for cardiac lesion treatments. They were there for other reasons as well. Specifically not all were infants.

THE COMMISSIONER: I somehow missed that in the course of this year's study if you can use digoxin for any other purpose.

MS. CRONK: It is my understanding, sir, you do not. The primary uses are, as we described them this morning. Dr. Phillips' evidence was that some of these patients had difficulties that were, predominant difficulties that were not purely cardiac in nature. They may, in fact, have been on digoxin for their cardiac problems, but they were there for other reasons as well.

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There is no doubt, sir, that all 37 were on the drug. The numbers breakdown in the following fashion, sir, and the breakdown in my submission is relevant. In 21 of the 37 cases the patients were known to have been suffering from some degree of renal failure at the time of death. In four more cases that was a possibility, Dr. Phillips was uncertain. There was the potential for renal failure in some 25 of the cases, and in fairness it was a certainty in 21. The highest post mortem level recorded in that entire patient group, or patient population, was the gutter blood study result of 169 nanograms to which I referred earlier, that was case number 5 on the gutter blood study. The second highest result was that recorded in the case of Gary Murphy, you will recall, sir, his level was 32. The third highest level recorded was 12.6 nanograms per millilitre, that reading was obtained from two patients. One of the two had been experiencing renal failure at the time of death, and on the second patient there was no ante mortem digoxin level available. So that in the first case, in my submission, the 12.6 reading, the fact that it was a high reading is potentially and reasonably explicable on the basis of the patient's renal failure as a well known cause for elevated digoxin levels.

EE-2

In the second case, sir, we don't in fact know what the ante mortem level was and it is impossible therefore to predict what in fact the multiplier was that applied in that case.

Drs.MacLeod and Phillips were both cross-examined extensively on the significance of the results recorded in these 37 cases. On the basis of their evidence, in my submission, it is clear from the study that the range of multiplier established is in fact in the order of two or three as seen in the literature. I say that sir for the following reasons: first in 23 of the 37 cases the ante mortem levels were taken 12 hours or more prior to death. In many cases they were in fact taken any number of days prior to death, that of course was the situation with Gary Murphy when the level was taken 19 days prior to death. As a result, in my submission, the true ante mortem level at or close to the time of death is not known and without that the range of elevation of digoxin in post mortem blood cannot be established.

Dr. MacLeod agreed, as did Dr. Hastreiter. Dr. MacLeod indicating that you cannot with confidence rely upon the apparent multiplier in those 23 cases.

Secondly, in 11 of the 37 cases there

EE-3

is no ante mortem digoxin level available at all. Obviously, once again you can't assess the range of post mortem multiplier if there is no denominator from which to measure it.

In the case of Gary Murphy where there was a level known some 19 days prior to death, Dr. MacLeod has testified that the time differential between the last ante mortem sample and the time of the post mortem sample is so long that in his view the post mortem level at least the multiplier reflected by that level is probably spurious, it is artifical, and in his opinion we really should ignore the Gary Murphy case as an example of the post mortem multiplier; that is found in Volume 64 at page 4466-4468.

So we have then sir, 23 cases where the levels were taken a long time before the time of death. We have 11 cases where there is no ante mortem level at all. That leaves us with three cases out of a total group of 37. In those three cases when the ante mortem level was actually compared to the post mortem level the multiplier is in the order of two or three as expressed by the literature. Dr. MacLeod agreed with that suggestion as did Dr. Phillips.

The issue then, sir, that is the basis for my submission that a reasonable and

EE-4

legitimate question of the range of multiplier is anywhere between zero and four, the highest being that reported in Dr. Hastreiter's most recent article published in April of 1983 and filed before you sir, as Exhibit 288.

The question then if in fact there is range when does it happen. Regret[illegible] the state of the art is such according to the pharmacologists that it cannot ever be said with certainty that the phenomenon has occurred unless the digoxin concentration close to the time of death is in fact known. Even where it is known, even when you do have an ante mortem level close to the time of death the evidence is it doesn't happen in all cases so you can't predict where it has happened and where it hasn't. The evidence from pharmacologists has been that the mere fact of a high level is not evidence that there was in fact a multiplier at all.

The illustration of the importance of this, sir, has to do with Dr. MacLeod's evidence as to whether or not it can in fact happen the other way. The majority of the evidence that you heard with respect to post mortem multiplier had to do with the fact that the concentration in blood would in fact increase. Dr. MacLeod, however, has suggested that

EE-5

there may be circumstances immediately after death where there may be some distribution of digoxin out of blood into the adjacent tissues resulting in a decrease in the post mortem blood level. That was Dr. MacLeod's evidence at the preliminary hearing and he repeated it here. It is found, sir, at Volume 63, pages 4134-4137. It was his opinion that if that occurred, the converse of the normal rule, it was likely to occur only where there had been a high concentration of digoxin in the blood at the time of death. This flows, in my submission, Mr. Commissioner, from the principle that digoxin when it does unbind flows from areas of high concentration to areas of low concentration. The implication of that proposition is obviously important. In any given child, and let us take for example the reading of 69 nanograms that we know was measured at the Centre of Forensic Science says on Allana Miller. On the one hand it might be postulated that that level, being a post mortem level, was in fact as much as four times higher than what her ante mortem level in fact had been. It could as well be one time higher because the range in my submission is anywhere from one to four.

If Dr. MacLeod's proposition is a legitimate one the level may in fact be lower than

EE-6

what the blood level was at the time of this child's death. This relates as well sir, to the evidence that you have heard as to the physiological activity in the body at the moment of cardiac arrest. Dr. Spielberg has testified that at the moment of arrest as distinct from death, various things can happen in the circulatory system. The first is asystole develops, that is no heart beat at all. In those circumstances there will be very little blood circulating. If, however, bradycardia has led to the cardiac arrest the blood will still be circulating although on a reduced basis. Similarly if there is a rapid ventricular rate blood will still be circulating notwithstanding that cardiac arrest has occurred but it won't be circulating as efficiently. Then finally if CPR, or cardio pulmonary resuscitation has been undertaken there is in fact, in Dr. Speilberg's opinion, a relatively good profusion of blood in the system.

Now the effect of that, sir, is that even after cardiac arrest, unless there is no heart beat at all some distribution of digoxin from blood into tissues is still occurring to a greater or less a degree depending on how much blood is still circulating. As I understand what Dr. MacLeod has

EE-7

said, he is of the view that if there is a very high concentration of the drug in blood at the time of arrest and at the time of death there may then immediately occur some further distribution, even after death, from blood to tissue for a short period of time, resulting in a decrease in the concentration of the drug in the blood specimen when it is tested for assay.

Dr. MacLeod has also given evidence as to another possibility which concerns him in interpreting the levels of these children. He said in cases where there is a high post mortem digoxin level in blood or serum, it may not be appropriate at all to apply the range of normal post mortem multiplier. That is, if in fact the range is properly said to be between 0 and 4 if you are talking about very high concentrations in blood, as we are in some of these cases; Justin Cook, for example, Allana Miller, arguably Kevin Pacsai, the multiplier in Dr. MacLeod's opinion can in fact be much lower he said as low as .25 per cent. Dr. MacLeod was quick to add this was really an intuitive opinion on his part there was no hard data which he was aware of to reflect that that inverse effect can in fact occur.

If the effect of all of this evidence,

EE-8

sir, both as to the possibility of an increase, the possibility of a decrease the possibility of a completely different range of multiplier applying when you are talking about high blood concentrations places us in my submission in this position. With every single one of these cases when you come to interpret the signficance of a high post mortem blood level there are four possible alternatives.

The first is the post mortem level is a true and accurate reflection of the level prior to death without any variation. That is no elevation has occurred at all and no decrease has occurred at all, that is the first possibility.

The second is that the post mortem level may be only slightly elevated over what the level was before death; that is on the basis of Dr. MacLeod's evidence.

The third possibility is that the post mortem level is higher by a fact of anywhere from 0 to 4 over the level prior to death.

The fourth possibility in my submission, sir, is that the post mortem level is in fact lower than the level for concentration prior to death.

If I could illustrate what I mean, sir, again with reference to Allana Miller's level.

EE-9

The level as mentioned at the Hospital for Sick Children was 78 nanograms on a post mortem blood specimen. That level may in fact, under these various propositions, be first the true level prior to death, that assumes there is no change at all. Secondly, it may be slightly higher than the level prior to death, meaning that the elevation was only as Dr. MacLeod suggested was possible .25 per cent and that the level prior to death could have been approximately 70.

THE COMMISSIONER: I'm sorry, .25 of 70 would be more than that.

MS. CRONK: Of 78, sir.

THE COMMISSIONER: The multiplier after death is .25 and .25 of the ante mortem would be --

MS. CRONK: I'm sorry, sir, we don't know the ante mortem, we are trying to work that from the post mortem to what the level at death was.

THE COMMISSIONER: I am sorry, the multiplier has to be from the ante mortem to the post mortem, you can't multiply that.

MS. CRONK: That's correct, sir.

THE COMMISSIONER: So .25 is .25 of what it was ante mortem. I am just really trying to

EE-10

break into your --

MS. CRONK: Trend of thought here, sir.

THE COMMISSIONER: If it was 70, a quarter of 70 is 17.

MS. CRONK: That's right, sir, the number is wrong, I'm sorry, sir, you are right.

THE COMMISSIONER: 70, if it was 70 you would get 87.

MS. CRONK: You are quite right, sir.

THE COMMISSIONER: It is more like 65, 64.

MS. CRONK: I will give you 65.

THE COMMISSIONER: Or 63.

MS. CRONK: Or 63. The point being sir, you are quite right and I apologize for my mathematics. The point is the level could in fact at the time of death still have been significantly high.

THE COMMISSIONER: That's right.

MS. CRONK: I will be pleased to accept for the purposes of illustration 63, 64, 65.

THE COMMISSIONER: All right.

MS. CRONK: The third possibility, sir, is that the level prior to death could have been lower by affect of as much as 4. The fourth

EE-11

possibility is that a level prior to death could have been higher than 78 nanograms, that it in fact decreased, and that again is on the basis of Dr. MacLeod's evidence. Having said, sir, I note the time and I suggest we take our break.

THE COMMISSIONER: All right, 20 minutes.

--- Short recess.

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--- On Resuming

THE COMMISSIONER: Yes, Miss Cronk?

MS. CRONK: Thank you, sir.

There are two points to which I would like briefly to return with both a smile and some chagrin. I spent so many days in the recent past understanding the merits of sodium potassium ATP ase that I forgot to deal with water. Plain water.

The question, sir, of what happens and why it is suggested as a hypothesis that when you boil a blood specimen the concentration of digoxin will be elevated is a much simpler explanation than the one I sought.

It appears, sir, Dr. Mirkin -

THE COMMISSIONER: Water will evaporate, is that the idea?

MS. CRONK: That's right. Just that simple.

THE COMMISSIONER: Digoxin being some kind of a substance that won't?

MS. CRONK: That is right, sir. As Dr. Mirkin explained it, in rechecking the transcript the suggestion is with some help from my friends that the water component of the specimen is that part of it which is subject to evaporation and if on boiling, and

I place emphasis on the boiling as opposed to heating, there is evaporation of the water, the volume of the specimen as I have suggested is altered such that there is a higher concentration of digoxin in the volume remaining after evaporation. When he takes a measurement at that point the theory is that it will be higher.

The evidence, of course, on that issue is that Dr. Mirkin is not in fact sure in his own mind that that can even occur, and he has testified as have others that heating alone will not effect a material change in concentration at all.

A second point to which I would like to return, sir, is the exercise I was undertaking immediately before the break, the suggestion of the application of Dr. MacLeod's various principles, the illustration being Allana Miller's post mortem digoxin level of 78 as measured at the Hospital for Sick Children.

There are as I have suggested in my submission, sir, four possibilities, and I would like to review them again if I might.

The first is that that post mortem level of 78 was in fact a true reflection of the level immediately before death. That is that there was no elevation caused by a post mortem multiplier effect nor

was there any decrease in the level caused under Dr. MacLeod's theory by immediate and continuing distribution from blood into tissues in the few minutes immediately after death. So the first possibility is that, sir, that is a hard true reflection of what the ante mortem level is.

The second possibility, sir, and this is the one in respect of which I had some difficulty a few moments ago is that if Dr. MacLeod's second position be a legitimate one, the level of 78 post mortem may in fact reflect an ante mortem level of 58.5. I would like to explain, sir, how that occurs.

Dr. MacLeod has suggested that the normal range of multiplier may be totally inapplicable in a situation where you have very high concentrations of digoxin and post mortem specimens. He is suggesting then that the normal range of as high as up to 4 may not apply and that it may be .25.

If that is the case, sir, it would mean ante mortem level of 58.5 elevated by a factor of .25 to a post mortem level of 78. That's the second possibility.

THE COMMISSIONER: I can always check your mathematics, but 58 is -

MS. CRONK: 58.5 elevated by a factor

of .25 resulting in a post mortem level of 78.

THE COMMISSIONER: I don't quite understand how that can happen.

MS. CRONK: All right.

THE COMMISSIONER: The most that a quarter of 58.5 would be would be 15.

MS. CRONK: That is right, sir, but we are talking percentages here, the issue being that if a level - all we have is a post mortem level of 78.

THE COMMISSIONER: All right.

MS. CRONK: If that reflects a quarter increase over what the ante mortem level was in effect it has gone up by 19.5 over the ante mortem level. That is the pure mathematics of it, sir.

THE COMMISSIONER: Well, they are impure mathematics to me because I just don't understand it. It goes up by a quarter. Isn't that what we're talking about? The post mortem multiplier is a multiplier of what it was ante mortem. Isn't that right?

MS. CRONK: That's right.

THE COMMISSIONER: It was ante mortem 58.5 and it goes up by 25%. It is going up at the most -

MS. CRONK: By 25% of 58.

THE COMMISSIONER: How do we get 78?

MS. CRONK: That is the other variation I am coming to, sir.

THE COMMISSIONER: All right.

MS. CRONK: The range - if you apply the various hypotheses, the very lowest that the ante mortem could have been is 19.7 nanograms. That would be the case, sir, working back - we only have the post mortem level to work back from.

THE COMMISSIONER: A quarter of 78.

MS. CRONK: That is right.

THE COMMISSIONER: Well, I knew that, yes.

MS. CRONK: The lowest level ante mortem (and that is of significance, sir, because of and in itself is a very high level) would be 19.7.

THE COMMISSIONER: That is right.

MS. CRONK: The highest it could have been ante mortem is in fact higher than 78, and I say that because Dr. MacLeod has suggested -

THE COMMISSIONER: I will accept all of that. The only thing I am having trouble with is the figure of 58.5, and it probably doesn't matter.

MS. CRONK: All right. I can try to explain it again, sir. You are quite right. Under

Dr. MacLeod's thesis if you assume an ante mortem level of X he is suggesting that - and it is a high level - he is suggesting that that may elevate only by as much as .25. You are absolutely correct, sir, you would then take 25% of X, add it to X and that would be the post mortem level.

Now under that hypothesis I am simply applying the mathematics and my submission to you is this: ignoring the 58, ignoring whatever factor it is, we are in this situation on Allana Miller's post mortem levels, and indeed all the others. There may be no elevation at all. The level may be real. It may in fact be 78. The level may be slightly - the level ante mortem may in fact have been more than 78 because Dr. MacLeod has suggested that some of it may have gone from blood to tissues and it may be lower, but I suggest to you, sir, that in Allana Miller's case on the reliable data before you it would never have been lower than 19.7 nanograms.

And, sir, I suggest to you that that potential for variation is really the only feature that comes out of this post mortem multiplier that affects the interpretation of these levels.

I don't know if that assists, sir, or adds to the conundrum. Yes to both?

FF-7

THE COMMISSIONER: No, I understand the 19.7. I simply don't think it is quite right either - within a couple of points, but I don't understand.

MR. STRATHY: If I could help my friend. Our calculation of X is 62.4 and then 125% of that is 78.

THE COMMISSIONER: I would settle for 62.4.

MS. CRONK: Mr. Strathy has got me back to where we were a few minutes ago and I think I can -

THE COMMISSIONER: No, you jumped from the 25% elevation to 4 times - 400% elevation, and with the 400% elevation you got 19 point - half of 78 is 39...It would be 19.5. If you want 19.7 that is fine by me, but if you take 78 as the eventual number, the first - did you say 62.7?

MR. STRATHY: 62.4.

THE COMMISSIONER: That seems dead on. You won't accept that?

MS. CRONK: I certainly will, sir. I certainly will. I am even more delighted that it comes with the assistance of Mr. Strathy. It may very well be, sir, that that number is a reflection of the

ante mortem level. As I suggest the proposition is simply we cannot with certainty on any of these levels say that there was a post mortem elevator. If you accept, sir, the evidence of Dr. MacLeod it may in fact work the other way.

May we come then, sir, with some relief on my part to the question of interpretation of levels for concentrations measured in tissue specimen? There are a number of general problems regardless of the type of tissue specimen involved. These have been outlined by Drs. Kauffman, Spielberg, Mr. Cimbura and others. I think they can be fairly summarized on the evidence in the following fashion: The first and most important general problem is that there is an area of tremendous overlap between concentrations in tissues associated with apparent toxicity and concentrations in patients taking digoxin without any signs of toxicity. That is there is a tremendous area of overlap between therapeutic and toxic ranges. That is so on whatever type of tissue specimen we are concerned with.

The second general problem, sir, is that there is a tremendous variation from individual to individual, and this relates, of course, to one of the basic concepts that has been advanced by the pharmacologists. It is related to a number of factors

such as age dependency, how old the patient is, what the clinical condition of the patient was, what the disease state was; the fact is that in some patients a particular level will produce toxicity and in others it will not.

The third general principle, sir, is that digoxin concentrations measured in tissues cannot be interpreted in isolation. They must be weighed in the context of the actual clinical condition of the child to determine the child's or the infant's disease state and whether the child was in fact exhibiting any symptoms consistent with digoxin toxication at the time of death.

Fourth, sir, the concentration measured -

THE COMMISSIONER: I am not sure I understand. You are going to come back to this, are you?

MS. CRONK: In some detail, sir. If I may on that third factor the point is that the level in tissue alone pharmacologists have said must not be viewed in isolation from the clinical circumstances surrounding the child.

In other words it is relevant to the interpretation of the level to know what was happening

with the child at the time the child died. Was the child, for example, demonstrating any clinical signs of digoxin toxicity? If so that is another piece of information that serves as an aid to interpreting the level and the degree of confidence that one places on your interpretation.

For example, Dr. Spielberg had said that the actual pathophysiology of the patient, the nature of the disease, and the child's response to corrective measures is important in assessing how significant some of these levels are.

The fourth general problem is then, sir, that once you have an actual concentration that has been measured in tissue, you have to take that level according to the experts and compare it with measurements that have been recorded in other cases to determine if it falls within the therapeutic or the toxic range.

In other words the number by itself doesn't help us very much. We have to look to what has been reported in the literature as being a level representative of a fatal poisoning case and a level representative of what can be demonstrated to take place in a child who is on digoxin therapy and who died from causes not attributed to digoxin toxicity.

Then finally, sir -

THE COMMISSIONER: We didn't do any of these things, though, did we?

MS. CRONK: Mr. Cimbura did, sir.

THE COMMISSIONER: Well, he had ranges.

MS. CRONK: That's right, sir.

THE COMMISSIONER: He never compared them with the child himself - herself or himself.

MS. CRONK: The purpose of calling the pharmacologists to give evidence, sir, to assist you in the interpretation of those levels was so that that exercise could be undertaken on the basis of actual levels measured by Mr. Cimbura.

You are quite right: he did have ranges. Those ranges were as I have suggested exactly in accord with that principle. They were based on reported cases of therapeutic levels and recorded levels in fatal poisoning cases. So that in each case - if for example, and I hesitate to return to Allana Miller, but if for example we take Allana Miller's level of 78 in a post mortem blood specimen, one of the ways we must interpret the level according to the experts is to take a look at what 78 in a post mortem blood specimen means in the context of post mortem blood ranges for children on digoxin therapy who have not died

from digoxin and what it means in levels measured in fatal poisoning cases and see where it falls in those ranges. That is really all the principle entails.

THE COMMISSIONER: Maybe so. I thought we were talking about tissue. I thought when we were talking about tissue -

MS. CRONK: It applies as well with tissue, sir.

THE COMMISSIONER: - Cimbura took some of these things and he said the range is let us say 250 to 750.

MS. CRONK: Yes, sir.

THE COMMISSIONER: And then this is a reading of 450 so it could be toxic and it could be therapeutic.

MS. CRONK: That is right, sir.

THE COMMISSIONER: But then he didn't go any farther and look at the child himself.

MS. CRONK: No, sir. That is what some of the pharmacologists who testified before you did.

THE COMMISSIONER: Should have, but they didn't do it. Did they do it?

MS. CRONK: Yes, sir, they did. Dr. Kauffman, for example and Dr. Spielberg for example.

THE COMMISSIONER: For this particular child?

MS. CRONK: That is right, sir. As did Dr. Mirkin. Dr. Mirkin's review team. As did Dr. Hastreiter. When I say look at the child, sir, it is obviously so they could not physically examine the child. I meant in that context they were to examine the child's chart and record the clinical history.

THE COMMISSIONER: Yes, all right.

MS. CRONK: And that in fact was done.

THE COMMISSIONER: All right.

MS. CRONK: And then a fifth general principle that relates to interpretation difficulty, sir, is that there are problems associated with the distribution characteristics of digoxin per se, and this by now perhaps is familiar ground, sir.

What is referred to there is, for example, infants and small children tend to have more digoxin in tissues than do adults. It is therefore difficult to extrapolate adult tissue concentrations to concentrations that are appropriate or inappropriate in infants.

For example, concentrations in tissues tend to be higher than in serum if the patient was exposed to digoxin therapy in the opinion of Dr. Kauffman

so that there are characteristics in a pharmacological sense of what happens to the drug that influence how these numbers should be interpreted. There are, however, a number of difficulties that are specific to the type of tissue quite distinct from tissues at large, sir.

Dealing with fresh or fresh frozen tissues first, Dr. Kauffman has testified that fresh and fresh frozen tissue levels reflect as close as can be obtained the digoxin concentration that existed in the tissue at the time of death.

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RD/cr

Nonetheless, all the general problems attendant upon interpreting tissue levels generally apply to fresh or fresh frozen tissue levels.

Mr. Cimbura has testified that the difficulties associated with the interpretation of levels found in tissues are much more complex than arise in the interpretation of concentrations found in post mortem blood. He has expressed the opinion that even when dealing with fresh tissues, unless the values of the levels measured are of very extreme proportions, the levels cannot, by themselves, without more, be regarded as conclusive of digoxin toxicity. They are, however, in some, sir, the best evidence available, as to what the concentration in tissue was at the time of the patient's death.

When I say, sir, that Mr. Cimbura has indicated that they cannot, of themselves, establish digoxin toxicity, he has, however, indicated that they can be of enormous assistance in identifying the presence of the drug, so that in a qualitative sense they can aid us, and I will return to this in determining that digoxin was, in fact, given to a particular patient.

THE COMMISSIONER: I would think they can do more than that, because surely the presence of

digoxin, unless it is for some reason would be discarded, no matter what kind of tissue it is, whether it is fresh or unfresh or put away in some kind of solution or something like that, will indicate the presence of digoxin, would it not?

MS. CRONK: It did, sir.

2 THE COMMISSIONER: So they are all qualitative?

MS. CRONK: That is right, sir.

THE COMMISSIONER: The fresh or fresh frozen are just more reliable qualitative, are they not?

MS. CRONK: That is correct, sir.

THE COMMISSIONER: Okay.

MS. CRONK: Mr. Cimbura's evidence in that regard, as I understood it, is consistent with that of the pharmacologists, that levels found in fresh tissues, as you suggested, are the most reliable amongst tissue specimens. They, of themselves, do not establish digoxin toxicity, but they can be supportive evidence for a conclusion of digoxin toxicity when coupled with other data. As well, as you quite rightly point out, they can establish the presence of digoxin just as can levels found in exhumed and fixed tissues. I will deal with

that in a moment.

THE COMMISSIONER: Yes, all right.

MS. CRONK: When we come to fixed or preserved tissues the problems are intensified, sir, as you know. Dr. Kauffman has testified when tissue is placed in fixative digoxin is soluble in a fixative and tends to be leached out in varying degrees from the tissue into the fixative solution. 3 To some degree then the digoxin can break down in the preservative solution so that the concentration of digoxin in the tissue, itself, may decrease.

Mr. Cimbura and Drs. Mirkin, Speilberg and Hastreiter, all agreed with that proposition and all agreed further that the ability to draw any firm conclusion regarding digoxin toxicity, based on levels from fixed tissues, is reduced by virtue of the potential for such degradation.

Mr. Cimbura again indicated, however, that digoxin concentrations measured in fixed tissues can provide and serve a vital function in serving a supportive data for a conclusion of digoxin toxicity when coupled with other toxicological pieces of information.

Dr. Mirkin was of the opinion, particularly, that in fixed tissues if the presence of

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digoxin was identified the level becomes obviously much more significant where the patient was thought not to have received digoxin during life.

Mr. Cimbura conducted a number of tests, sir, and, in my submission, are of assistance to you in assessing the legitimacy of these various opinions. Specifically he conducted a test to determine the degree of degradation in concentrations of digoxin in tissue when they are placed in fixative or preservative solution.

The results of that particular study, sir, are set out in Exhibits 213, page 11, page 13 and page 14. Briefly they can be summarized as follows: His first experiment was to test the concentration of digoxin in tissue before it was placed in preservative solution and that is, of course, either Klotz or Ely solution, as it has been referred to and then to test the concentration and the tissue after it had been in a fixative solution for some period of months.

On the first study it was kept in a fixative solution for six to nine months and Mr. Cimbura's results indicate there can be marked reduced concentrations of the drug in the tissues that have been fixed for that length of time. That,

sir, is the study set out in Exhibit 213, page 11 and page 13. He did a similar test, sir, taking only portions of various tissues. The first study took the whole organ, a significant tissue sample. He did a second study taking portions of the tissues and did exactly the same thing, measured the amount of digoxin in the fresh tissue before it was placed in the fixative and then measured the amount in the tissue after it had been placed in the fixative, but this time it had been stored for only a period of one to two months, a much shorter length of time. He again found marked reduction in the concentrations in the fixed tissue after one to two months over the concentrations in the fresh tissue. These, I should say, sir, these tissue specimens came from the same organ and the same patient.

Despite all of the difficulties presented by the possibility of degradation the pharmacologists all agreed, as did Mr. Cimbura, that the digoxin concentrations measured in tissues of this kind do establish that the patient received digoxin during life. That is the qualitative value that I have spoken about, sir, and that digoxin was present in the tissues tested after death.

In short, sir, in those four patients,

whom we know were not known to have received prescribed doses of digoxin, the levels in fixed tissues establish two things, first of all, that digoxin was present and, secondly, that they received an unprescribed dose of digoxin, be it by accident or be it deliberate.

Mr. Cimbura undertook another exercise with respect to fixed tissue as well, that is in my view, fundamental to understanding what his results mean. He attempted, sir, you may recall, to estimate from the values measured in fixed tissues what the values or concentrations of the drug was in fresh tissue at the time of death.

As you may recall, sir, he did this by utilizing a five step procedure. First, he analysed the preservative or fixative for digoxin content when the tissue arrived at his laboratory already preserved. He looked at the solution itself, and analysed that.

Secondly, he analysed control samples of various kinds of preservative solutions, Klotz and Ely, to know what one would normally find in those solutions. Essentially he measured the concentration of digoxin in the Klotz solution plus the volume, the amount of the solution. He multiplied

the two together and the resulting product was an estimate of the concentration of digoxin in the fixative solution, as a whole.

The fourth step, sir, was to divide that number by the weight of the tissue, itself, and he knew that, sir, from the autopsy reports that were provided. In doing that he arrived at an estimate of the concentration of the drug per gram of wet tissue in the original tissue at the time of death. By adding to that, the measurement he obtained on an RIA assay of the concentration of digoxin-like substances, he was able to estimate a concentration per gram in the original fresh tissue at the time of death.

Although the mechanics of the process may not be of any intimate interest to any save scientists, Mr. Commissioner, I can fairly say this, that Mr. Cimbura regarded this approach as a very conservative one and he found support for that view from Dr. Hastreiter and others. Dr. Hastreiter further testified it was quite appropriate for Mr. Cimbura to have undertaken the exercise at all and many of the pharmacologists, who testified before you, indicated that those estimates can serve as a worthy benchmark of what, in fact, was present at

the time that the child died.

8 We come then, sir, to the third and final type of tissue specimen which we are concerned, that is exhumed or embalmed tissues and again there are problems of interpretation that are particular to that kind of tissue specimen.

The concerns that arise with respect to fixed tissues, that is the possibility of degradation of the tissues in the body, arises again with respect to exhumed tissues, but this time for a different reason. It is not obviously because of any fixative or preservative solution, but rather the possibility arises because of the embalming or the burial process and, as well, the length of the time that the body was buried before the tissue specimen became available for assay.

There are, as well, two additional concerns, according to Dr. Kauffman. First, virtually nothing is known in a pharmacological sense about the pattern of redistribution of digoxin in tissue over a long period of time after death. The longer the patient was buried before the exhumed tissue specimen was made available the greater the degree of uncertainty as to what, in fact, happened to digoxin, if it was present in the body over that period of

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time.

The second area of difficulty voiced by Dr. Kauffman is that tissues become desicated over time. This is not dissimilar, sir, to the boiling problem that we spoke about earlier, that is that over time tissues become drier and drier, depending on the burial conditions, and again the length of time that the body was buried. Digoxin concentrations in tissues are measured in terms of tissue weights. Accordingly, if water is lost from the tissue by the drying process the weight of the tissue is diminished and digoxin concentrations may appear higher, because the tissue being measured weighs less. That's a second problem according to Dr. Kauffman. His evidence in that regard, sir, is found at Volume 70, commencing at page 5479.

Once again, sir, despite all of those difficulties the pharmacologists and Mr. Cimbura are agreed that concentrations properly measured by an appropriate analytical technique in exhumed tissues can, with reasonable scientific certainty, establish one way or another in a qualitative sense the presence of digoxin and, therefore, whether or not the particular patient received digoxin prior to death.

In an effort to explore further the

various difficulties that arise with exhumed and embalmed tissues, and particularly embalmed tissues, Mr. Commissioner, Mr. Cimbura undertook another series of studies. These, as well, are set out in Exhibit 213. What he did in this case was similar to what he undertook to test the effect of fixative solution. He effectively conducted a study on various kinds of embalming fluids provided to him from various funeral homes in the city to test the degradation proposition. The results specifically are set out on page 12 of Exhibit 213. Once again he found a marked decline in digoxin concentrations over time and tissues placed in embalming fluid.

The net of all these difficulties, Mr. Commissioner, in my submission, is as follows: First, as you said a few moments ago, a very much higher degree of confidence may fairly be placed on the significance of digoxin concentrations measured in fresh or fresh frozen specimens than on concentrations measured in fixed or exhumed or embalmed tissues.

Secondly, although levels measured on the fixed and exhumed tissues are problematic in any number of ways due to the possibility of degradation, they are invaluable in a qualitative sense to determine the presence of digoxin and, secondly, they can serve

11 as potentially supportive data where other toxicological or clinical data exists.

As you know, sir, it is my intention to deal with the actual measurements that were made on these various blood and tissue specimens for these children. Before doing so, however, there is one other aspect of the difficulties of interpretation that arise. This is one, sir, that properly speaking is a matter that flows from a pharmacological issue and it is the relationship between serum potassium levels and serum digoxin levels.

Once again, there is an area of agreement between the experts who have testified before you and a pronounced area of disagreement. It arises specifically, sir, with relevance to the case of Kevin Pacsai. I will explain why in due course.

There is agreement, though, on the following issues: First, abnormally low potassium levels will pre-dispose an individual to toxicity from an amount of digoxin lower than what would otherwise be required or expected to produce toxicity. That is the opinion of Drs. Rowe, Costigan, Kauffman, Mirkin and Speilberg.

Second, there appears, as well, to be a concensus that elevated serum potassium levels are

known to accompany elevated serum digoxin concentrations.

THE COMMISSIONER: Say that again.

MS. CRONK: High potassium levels accompany high digoxin levels. The two can and are frequently taken together. As Dr. Kauffman points out, that is not a consistent finding in cases of digoxin intoxication. In other words, you can have high digoxin levels but not see high potassium levels. It is just that very often you see the two together. It doesn't universally happen.

That, sir, is the opinion again of Dr. Rowe, Dr. Bain, Dr. Speilberg and Dr. Kauffman.

The third principle upon which there is agreement, sir, is that elevated digoxin levels, high digoxin levels can and do cause in certain circumstances elevated potassium levels, although once again it doesn't occur in all cases.

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That translates, sir, to my simple mind to this. If you have high digoxin levels and high potassium levels it is clear on the reported literature and in the scientific community that the high digoxin levels could have caused the high potassium levels. That is the opinion of all of the pharmacologists, and as well, Dr. Hastreiter. That seems to be the departure point sir, from which controversy then arises. The area of disagreement flows from the converse proposition and that is this. The hypothesis that elevated potassium levels in and of themselves can cause elevated digoxin levels. Recognizing once again that very often the two are seen together.

You will recall, sir, and those of us not intimately familiar with the medical lexicon that hyperkalemia is a term applied to abnormally high potassium levels, hyperkalemia. Hypokalemia is a term applied to abnormally low potassium levels .

Dr. Kauffman has testified that the normal range for a potassium level in an infant is between 3 and 5.5. The cardiologists, as I apprehend thei evidence, do not disagree with that as a general statement of a normal range.

There are a number of clinically recognized courses of elevated potassium levels and

HH-2

these become important sir, again in the context of the case of Kevin Pacsai and as well as Stephanie Lombardo and Kristin Inwood, because the last two children were clinically recorded as having high potassium levels at the time of their deaths. There are then a number of recognized causes.

The first, it may be indicative of a result of some kind of renal failure, that was the opinion of Dr. Costigan at Volume 45, page 44 and Dr's Kauffman and Spielberg.

Secondly it can be the result of acidosis, that is the opinion of Dr's Kauffman and Spielberg.

Thirdly it can result, according to Dr. Spielberg from necrosis or tissue injury, death of tissue cells or injury to tissue cells.

Fourth it can result from hypoglycemia a sugar deficiency in blood, or from hypoxia and oxygen deficiency, and that was the opinion of both Dr's Kauffman and Spielberg. So this can be added, sir, to the obvious fifth, known and recognized cause and that is high digoxin levels. There are accordingly a number of circumstances which can in and of themselves produce high potassium levels other than high digoxin levels.

HH-3

The issue as to whether or not the high potassium levels can cause high digoxin levels is important, because Dr's Kauffman and Spielberg have suggested that they think that proposition to be a legitimate one. Dr. Spielberg in fact has advanced it as a possible explanation for the levels in Kevin Pacsai's case. This is the area of disagreement however, because neither Dr. Kauffman nor Dr. Hastreiter were aware of any empirical data or reported cases in the literature that substantiated the proposition. Dr. Bain in his report of these cases, which you will recall sir, is Exhibit 48, agreed and acknowledged that there was no reported or empirical data to support the proposition.

Kevin Pacsai, sir, you may remember had high potassium levels measured at three different hospitals; at St. Joseph's Hospital in Toronto, at McMaster in Hamilton and subsequently at the Hospital for Sick Children on admission there.

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/DM/ko

At McMaster sir the levels, and perhaps we should start with St. Joseph's the earliest level; on March 7th sir the level of 7.4 at St. Joseph's Hospital, that is found in Exhibit 278.

THE COMMISSIONER: St. Joseph's Hospital, is that in Toronto or in Hamilton?

MS. CRONK: It is in Toronto, I understood it was in Toronto.

MR. SHINEHOFT: It is in Hamilton.

MS. CRONK: Thank you, I am grateful. The level was 7.4, sir, that is on the 7th of March. The child you will recall died at 10:10 in the morning of the 12th of March. He went from St. Joseph's Hospital to McMaster Hospital and a series of levels were measured there. On the 8th of March he had levels of 5.6, 4.6, 3.1, 4.5 and 4.1, the 4.5 specimen was a slightly hemolyzed specimen which the pharmacologist have indicated makes the validity of the level questionable. On the 10th of March, still at McMaster, he had a level of 3.9. On the 11th of March the level was 5.8, again at McMaster. It is that day, sir, that he was admitted to the Hospital for Sick Children and although he had a level earlier in the day of 5.8 he had a level of 3.9 taken approximately two hours after admission at the Hospital for Sick Children.

H2.2 The next morning, the morning of his death, a test and sample were taken at 6:30 in the morning in the Intensive Care Unit, his level at that time was recorded as 9, but that sample again was slightly subject to hemolysis and there is some question therefore as to its validity. But a sample was taken approximately an hour later, sir, at 7:20 in the morning, some three hours before he died, and the level was 7.7. It is clear, therefore, sir, that the child's potassium level at St. Joseph's was clearly very high. Dr. Kauffman expressed the opinion that the child at that point was really almost dead. He was very acidotic however. He also had a sugar deficiency and an oxygen deficiency that were recorded clinically, any one of which could have caused the elevation in his potassium level. By the time the child reached McMaster and during his stay there the level had fallen and continued to fall and on March 11th he was back up to 5.8, and was clearly fluctuating. At the Hospital for Sick Children the levels recorded on the morning of March 12th, the morning of his death, were clearly of concern, and I suggest, sir, the real level at issue is that of 7.7. You may remember that in the medical chart of Kevin Pacsai Dr. Costigan, who was with the child in the

H2.3

Intensive Care Unit, expressed his concern that the child's level in something less than 12 hours could go from 3.9 to 7.7, although no potassium had been prescribed nor known to be administered to the child.

Dr. Spielberg testified that the high potassium level could be accounted for by digoxin toxicity. The child's diseased state was something which is not yet fully understood. His evidence at Volume 57, page 2714. Drs. Kauffman and Hastreiter thought the most likely explanation for the digoxin toxicity, recognizing that that is a historically legitimate cause for elevated potassium levels. Dr. MacLeod also thought that the administration of digoxin to the child could have accounted for the elevated potassium. Dr. Spielberg alone, on my understanding of the evidence, suggested the reverse, that the elevated potassium levels could have caused the elevated digoxin levels.

In my respectful submission, sir, while it must be recognized as a possibility, as a hypothesis put forward by well respected and qualified pharmacologists, the hypothesis should be rejected as not being a probable explanation for Kevin Pacsai's digoxin levels. I make that submission to you, sir, for the following reasons.

HH2.4

First, Dr. Spielberg alone is noted amongst the pharmacologists to have advanced his thesis as an explanation for those digoxin levels. Even he ranked it, sir, as only a possibility, relying more heavily on what he described as the child's general overall path of physiological condition of which elevated potassium levels were a part.

Secondly, as confirmed by Drs. Kauffman and Hastreiter and Bain, and I suggest implicitly by Dr. MacLeod, there is no empirical data or reported literature to confirm or suggest that the phenomenon could even occur.

Third, in my submission, there is a compelling well recognized alternate explanation that digoxin could have caused the elevated potassium levels and for that reason the two in this case were seen together.

Fourth, and I place less emphasis on this submission, sir, the child had clearly demonstrated an earlier clinical history of elevated and fluctuating potassium levels, yet on March 9, 1981 his digoxin level at McMaster was 1.8 nanograms. In short, although he had experienced elevated potassium levels before, the only ante mortem level prior to

HH2.5

arrival at the Hospital for Sick Children and his death was 1.8, perfectly normal within the therapeutic range.

Sir, I propose now to turn to the actual levels that have been found in these children. By way of assistance I have prepared a chart which sets out the ante mortem and post mortem blood levels of each child as recorded anywhere, at any institution or at the Centre of Forensic Sciences, and as well sets out the actual levels in the various tissue specimens. There are a number of general matters with respect to these levels, sir, and I think I can cover one or two of them before we break for the day, and then we can deal with the actual levels tomorrow.

THE COMMISSIONER: Yes, all right.

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HH-3-1

There are a number of children for whom detailed charts of this kind have not been made. There are in fact 14 children for whom no digoxin data is available or for whom only incomplete data is available, and there is a separate chart, sir, I think a copy has been provided to you and it has to other counsel, that sets out the name of these children, and the only known digoxin information with respect to them. This is a list of some 14 children, sir. It indicates their name, the date and time of their death, their known ante mortem digoxin levels measured within the last two weeks of life. I admit, sir, I arbitrarily took that cut off point because in some instances the particular child had been hospitalized for a very lengthly period of time and there were a great number of digoxin levels recorded. Finally you will note, sir, that in each case no post mortem digoxin level be it on blood or tissues is available. It is with respect to these children that I was talking a moment ago to make certain general observations.

The first is that all these children were either on digoxin therapy at the time of their death, or were known to have received prescribed doses of digoxin at some time during their life.

Secondly, if the therapeutic range for

HH-3-2

ante mortem digoxin blood sample for an infant is accepted, as I have submitted to you on the evidence it should be, as anywhere between 0 to 3, or 3.5 nanograms per millilitre, only two of these readings are above the therapeutic level. I draw your attention there, sir, to the level accorded on Real Gosselin on December the 17th, 1980, a level of 3.7 nanograms; and a level recorded on Richard McKeil on October the 14th, 1980, effectively the day of the night that he died the level was greater than 4.7 nanograms.

To assist you there, sir, in the case of Real Gosselin you will recall that the evidence of both Dr's Rowe and Freedom was that the child received the digitalizing doses at the referring Hospital in Winnipeg larger than under normal circumstances would have been administered at the Hospital for Sick Children. It was possible therefore that the slightly elevated level could be attributed to the slightly larger than usual, in the opinion of those cardiologists, doses administered at that Hospital.

We come to the case of Richard McKeil sir, and you will recall that I made a submission to you early in the day that there was absolutely no evidence whatsoever to suggest that any of the blood samples taken from any of these 36 children was taken

HH-3-3

prematurely in point of time in relation to the last dose. The exception was Richard McKeil. The evidence in his case is that the last dose of digoxin administered to him prior to his death was at 6:00 a.m. on October the 14th, 1980, this is at page 90 of his medical chart and the sample which resulted in this level of greater than 4.7 was taken at 9:40 a.m. the same morning, that is three and a half hours later.

It is clear on the basis of the evidence of Dr. Rowe and as I recall it, Dr. Bain, that the relationship in time, the temporal relationship you could account for that elevated level. You will hear from Mr. Lamek's submissions in other respects as to what might also account for the symptoms the child was exhibiting and the level itself, but those are the two that stand out on this list.

That leaves us then, sir, with 22 cases where there is data available and it comes from one of three sources; from the Hospital for Sick Children on blood specimens only; from the Centre of Forensic Sciences on blood and tissue specimens; and in a few cases from other hospitals, that is from the referring hospital in one case, Kevin Pacsai from Mt. Sinai, and in one case from Toronto General Hospital

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in the case of Justin Cook.

May I propose, sir, that we rest there for today and deal with the actual levels tomorrow.

THE COMMISSIONER: Yes, all right. Then until 10:00 tomorrow morning.

---Whereupon the hearing adjourned at 4:30 p.m. until 10:00 a.m. June the 6th, 1984.